THE PROGRAMS OF THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

AN ADMINISTRATIVE REVIEW

SEPTEMBER 1986

U.S. DEPARTMENT OF HEALTH AND
HUMAN SERVICES
Public Health Service
National Institutes of Health

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REPORT OF THE COMMITTEE FOR ADMINISTRATIVE REVIEW OF THE PROGRAMS OF THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

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INTRODUCTION

On November 20, 1985, the Congress passed Public Law 99-158, the Health Research Extension Act of 1985, which established a new National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). In effect, this legislation divided the former National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) into two institutes--the NIAMS and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which is comprised of those programs of the former NIADDK that were not transferred to the new NIAMS.

The Act required that, within 1 year of enactment, there be conducted "an administrative review of the disease research programs of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to determine if any of such programs could be more effectively and efficiently managed by other national research institutes." In response, the Committee for Administrative Review of the Programs of the National Institute of Diabetes and Digestive and Kidney Diseases was established by the Director, NIH, and charged with the responsibility to conduct such a review.

Specifically, the Committee--comprised of senior NIH staff, augmented by expert consultants--was asked to:

- review the current administrative structure of the NIDDK to assure that recent program realignments resulting from the creation of the new institutes have not resulted in inappropriate or ineffective organizational arrangements;

- identify any factors that may be operating within the current organizational structure to reduce the effectiveness of the scientific programs;

- determine whether evidence exists to suggest that the growth, development, and scientific productivity of any of the scientific programs placed within the present structure of the NIDDK would be enhanced if administered or conducted by some other component of the NIH; and

- assess the degree to which the present administrative framework provides an integrative focus for the existing broad array of scientific programs and suggest any modifications that would improve program performance.

As part of the discharge of the responsibilities, the Committee met on July 1, 1986, in Bethesda to conduct deliberations and formulate findings and recommendations. During that meeting, the Committee listened to briefings by NIH staff designed to provide information on (1) the organizational structure of the current programs of the NIDDK and the nature of the scientific activities carried out within those programs; (2) the types of scientific activities being conducted in other Institutes which relate to the programs of NIDDK; and (3) the nature of the guidelines that are employed by the Division of Research Grants, at NIH, in assigning grant applications to the NIDDK, with

particular emphasis on the criteria that are used to distinguish between the program areas of relevance to that Institute and those programs of other Institutes that may border on the programs of the NIDDK.

In addition, the Committee conducted a public hearing in which it was afforded the opportunity to hear the views expressed by representatives of professional societies and voluntary health organizations concerning the appropriateness of the current structure of the NIDDK.

It was against this backdrop that the Committee formulated the following views, opinions, and recommendations.

OBSERVATIONS AND RECOMMENDATIONS

Organizational Structure

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) was created after a period of prolonged and intensive scrutiny of the programs of the parent National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), which was marked by a progression of organizational changes culminating in the recent establishment of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). In view of this long history of organizational uncertainty, the Committee feels that every effort should be made to create a stable environment for the administration of the current programs of the NIDDK. Accordingly, the Committee believes that there should be a presumption against additional organizational changes unless compelling evidence exists to support such changes.

At the outset, the Committee wishes to underscore its major conclusion that the current organizational structure of the NIDDK provides an adequate and appropriate setting for the full array of scientific programs presently placed within the purview of that Institute.

The Committee found that the transfer of programs attendant upon the creation of the new NIAMS did not destroy the internal logic and cohesiveness of the remaining structure of the NIDDK. To the contrary, it was found that the present administrative framework continues to provide an integrative focus for the set of scientific programs that remain in the NIDDK. In fact, the four major disciplinary components of the NIDDK--metabolism, nutrition, endocrinology, and immunology--provide a common scientific undergirding for much of the categorical disease research for which the Institute has primary responsibility.

In addition, the Committee could find no structural impediments within the current organizational structure of the NIDDK acting to retard progress or reduce the effectiveness of the scientific programs. Conversely, nothing was found to suggest that the growth, development, and scientific productivity of any of the scientific programs placed within the present structure of the NIDDK would be enhanced if administered or conducted by some other component of the NIH.

Philosophically, the Committee feels that a strong argument could be made for the transfer of a particular program to a different organizational milieu if that program were operating in an inhospitable organizational setting which was inimical to the growth and development of that program. In the case of the NIDDK, however, the Committee could not detect the existence of any institutional bias acting to provide favorable treatment for some programs at the expense of others. It appears, in fact, that each of the programs within the current organizational structure has equal opportunity to flourish on the basis of its own merit.

For the above reasons, the Committee believes that further organizational changes are unnecessary and would merely increase the risk of fragmenting scientific effort, restricting communication, adding to the burden of program coordination, and prolonging organizational instability.

Plurality of Support

Clearly, many of the diseases and areas of research for which the NIDDK has primary responsibility are also of interest to many of the other categorical Institutes and, in fact, receive additional research support from these various Institutes. The Committee believes that valid reasons exist for employing multiple sources of support and that this practice has a salutory effect in promoting progress within these areas. The great diversity in the orientation of the various Institutes that share these areas of common interest serves to prevent wasteful duplication of effort and, instead, assures that adequate attention and support is focused on the full range of research approaches and perspectives that can be brought to bear on these important research areas. Accordingly, the Committee believes that no useful purpose would be served by attempting to effect organizational changes designed solely to achieve consolidation of responsibility for a particular research area within the administrative aegis of a single Institute.

Within such systems of multiple support, however, a constant need exists to assure effective coordination among the various components that share an interest and responsibility in a particular area of research. In this respect, the NIDDK appears to maintain an impressive variety of mechanisms for coordinating program activities. These mechanisms range from legislatively mandated interagency coordinating committees responsible for facilitating communication among all Federal agencies directly or indirectly involved in selected disease areas to trans-NIH coordinating committees established to (1) provide a forum for the exchange of information and views; (2) strengthen and improve information systems for reporting on research and related activities in selected areas of special interest; (3) identify opportunities for initiation of special programs; and (4) provide a focus and central point of contact for the NIH in interactions with other Federal agencies and outside organizations.

Where a sufficient commonality of interest exists among the Institutes, the function of the committees often extends beyond the role of information exchange and coordination and, in fact, involves the active promotion of collaborative activities through the sponsorship of shared activities involving the joint development of goals, plans, and programs. In such instances the committees serve to (1) promote the development of joint program announcements

and requests for applications (RFAs) to alert the scientific community to specific goals, research needs, special funding plans, and opportunities in specific areas of research; and (2) facilitate the joint sponsorship of workshops, conferences, and symposia designed to identify areas of research need and to stimulate research in areas of highest priority.

Although current arrangements for achieving coordination appear to be adequate, the Committee recommends that constant monitoring of program activities be conducted by the NIDDK for the purpose of identifying new and emerging areas requiring additional coordination.

Views from the Public Perspective

One useful indication of the efficiency and effectiveness of an organization's programs is provided through the views and opinions of those constituency groups who champion the causes served by those programs. The Committee had a rewarding opportunity to sample such views through the conduct of a public hearing. A notice of the hearing was published in the Federal Register to communicate the nature of the study under way and to invite the participation of interested parties. As a result of this effort, eight witnesses--representing a broad spectrum of professional societies and voluntary health organizations--presented testimony at the hearing and many others provided written testimony for the record.

The general tenor of the testimony provided by the public witnesses was entirely consistent with the principal findings and recommendations of this Committee. On the whole, these views represented a resounding endorsement of the current organizational structure of the NIDDK, the scientific and managerial capability of the staff of that Institute, and the general environment that exists within the NIDDK. The Committee heard no suggestions for alternative organizational arrangements to increase scientific productivity and health improvement within the categorical areas served by these programs.

The Committee notes, however, that several witnesses suggested further changes in the name of the Institute to provide added visibility to various selected program components. The Committee believes that consideration of such suggestions is clearly outside its purview, and individuals or organizations wishing to pursue such goals should seek other, more appropriate, avenues for effecting such changes.

CONCLUSION

After examining the programs of the NIDDK, reviewing the programs of the other Institutes that relate to the programs of the NIDDK, and hearing testimony from representatives of professional societies and voluntary health organizations, the Committee has concluded that the current organizational structure of the NIDDK provides an adequate and appropriate setting for the scientific programs that are housed within that Institute and that no further organizational changes are required or desirable at this time. The Committee feels confident that the programs of the NIDDK will be afforded every opportunity to thrive, consistent with the levels of funding generally available for biomedical research, and it looks forward to the continued scientific productivity and accomplishments that have characterized these programs in the past.

SEC. 10. REVIEW OF DISEASE RESEARCH PROGRAMS OF THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES.

The Secretary of Health and Human Services shall conduct an administrative review of the disease research programs of the National Institute of Diabetes and Digestive and Kidney Diseases to determine if any of such programs could be more effectively and efficiently managed by other national research institutes. The Secretary shall complete such review within the one-year period beginning on the date of enactment of this Act.

COMMITTEE FOR ADMINISTRATIVE REVIEW OF THE PROGRAMS OF NIDDK

NIH Staff

Dr. Thomas E. Malone (Chairman)
Deputy Director, NIH

Dr. William F. Raub
Deputy Director for
Extramural Research and Training, OD

Dr. Jay Moskowitz
Associate Director for
Program Planning and Evaluation, OD

Dr. Alan Rabson
Division of Cancer Biology and Diagnosis
National Cancer Institute

Consultants

Carl W. Gottschalk, M.D.
Professor of Medicine and Physiology
Division of Health Affairs
University of North Carolina
Chapel Hill, NC

Kurt J. Isselbacker, M.D.
Mallinckrodt Professor of Medicine
Massachusetts General Hospital
Boston, MA

Robert J. Lefkowitz, M.D.
Investigator, Howard Hughes
Medical Institute
James B. Duke Professor of
Medicine and Biochemistry
Duke University Medical Center
Medical Science Building 1-B
Durham, NC

Edward D. Horton, M.D.
Professor and Associate Chairman of
Medicine
Division of Endocrinology, Metabolism
and Nutrition
Department of Medicine
Given Medical Building
Burlington, VT

David M. Kipnis, M.D.
Busch Professor and Chairman
Department of Medicine
School of Medicine
Washington University
St. Louis, MO

Paul A. Marks, M.D.
President
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY

Executive Secretary

Mr. Edward Lynch
Program Planning and Evaluation, OD, NIH

APPENDIX A
Overview of NIDDK Programs

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ADMINISTRATIVE REVIEW OF THE PROGRAMS OF THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES (NIDDK)

On November 20, 1985, the Congress passed Public Law 99-158, the Health Research Extension Act of 1985, which established a new National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). In effect, this legislation divided the former National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) into two institutes--the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which is comprised of those programs of the former NIADDK that were not transferred to the new NIAMS, and the NIAMS.

The Act requires that, within one year of enactment, there be conducted "an administrative review of the disease research programs of the National Institute of Diabetes and Digestive and Kidney Diseases to determine if any of such programs could be more effectively and efficiently managed by other national research institutes." A Committee for Administrative Review of the Programs of NIDDK has been established and charged with the responsibility to conduct such a review.

This document has been prepared to provide the necessary background material. It describes the Institute's mission, program strategy, structure, operations, scientific programs in detail, and, in an appendix, specific examples of research projects from each of the Institute's programs.

We hope that this compendium will prove informative and helpful to the Review Committee in the fulfillment of its task.

Pierre F. Renault, M.D.
Acting Director, NIDDK

I. NIDDK MISSION AND STRATEGIES

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MISSION

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports research on many of the most serious diseases affecting the public health. The Institute's mission includes both basic and clinical research on these diseases, among which are diabetes, endocrine and metabolic disorders including cystic fibrosis; digestive diseases and nutritional disorders; and kidney and urinary tract diseases and blood disorders. Basic research is conducted and supported in such areas as endocrinology, genetics, metabolism, biochemistry, physiology, molecular biology, pathology, and pharmacology.

The Institute supports basic and clinical research through investigator-initiated grants, program project and cancer grants, and career development and training awards. In addition, it supports research and development projects and large-scale clinical trials through grants, contracts, and cooperative agreements. The Institute's division of intramural research conducts basic studies in endocrinology; genetics; chemistry; biochemistry; metabolism; physical, chemical, and molecular biology; chemical physics; pharmacology; and pathology. Its scientists also guide clinical research and treatment programs on diabetes, other metabolic diseases, cystic fibrosis, endocrine disorders, digestive diseases, kidney diseases, and blood disorders.

Exhibit 1 shows representative examples of NIDDK research areas.

The focus on basic research which has traditionally guided NIDDK's programs is grounded in the fact that a fundamental understanding of the intrinsic nature of each disease is imperative for the development of effective strategies for prevention and therapy--and the work of the Institute involves many chronic and progressive diseases with as yet unknown etiologies. Advances in basic knowledge are continually and productively expanded into appropriate clinical studies and trials, and into programs of technology transfer and information dissemination to the community of biomedical researchers, to the practicing physician and to the public in order to contribute promptly to the improvement of the nation's health. The Institute's research is of profound importance to the public health since no subgroup of our population is immune to attack by the diseases which NIDDK addresses. Their collective economic burden exceeds $100 billion annually; the more profound cost of these diseases in terms of human suffering cannot be measured.

The impact of some of these diseases is indicated in Exhibit 2, which shows the prevalence, or number of affected individuals in the United States and the estimated economic costs to the American public.

Finding effective methods to prevent, control, and treat these diseases and disorders, through its various research programs and activities, is the mission of the NIDDK.

DIVISION OF DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES

Diabetes

- Insulin-dependent diabetes
- Noninsulin-dependent diabetes
- Complications of diabetes
- Etiologic factors in diabetes
- Immunology and diabetes
- Insulin receptors
- Insulin resistance
- Insulin delivery devices
- Pancreatic islet cell transplantation
- Nutrition and diabetes
- Animal models of diabetes

Endocrine Diseases

- Disorders of endocrine glands (thyroid, pituitary, etc.)
- Hormone synthesis, secretion, action, and interactions
- Hormonal imbalances
- Research availability of hormones
- Growth factors
- Recombinant DNA production of peptide hormones
- Neuroendocrinology and brain peptides
- Hormones and pharmacotherapy

Metabolic Diseases

- Inborn errors of metabolism
- Animal models of inborn metabolic errors
- Cystic fibrosis
- Enzyme structure and function
- Cellular oxidation and biological membranes
- Cell surface receptors
- Reye's syndrome
- Noninvasive instrumentation in metabolic research

DIVISION OF DIGESTIVE DISEASES AND NUTRITION

Esophageal, Gastric, and Colonic Diseases

- Ulcer disease
- Functional bowel disorders
- Gastrointestinal motility dysfunctions
- Inflammatory bowel diseases
- Gastrointestinal bleeding
- Endoscopy in research, diagnosis, and treatment
- Gastrointestinal growth and regeneration
- Structure, function, and disease of the esophagus and stomach
- Anal-rectal diseases and disorders

Intestinal and Pancreatic Diseases

- Gastrointestinal hormones
- Small intestine structure and function
- Intestinal digestion, absorption, and secretion
- Malabsorption syndromes
- Diarrheal diseases, celiac sprue
- Structure and function of the exocrine pancreas
- Pancreatitis
- Small intestine and pancreas transplantation
- Salivary gland structure, function, metabolism, and diseases

Liver and Biliary Tract Diseases

- Hepatitis
- Cirrhosis
- Genetic liver disease
- Hepatic transport defects
- Cholesterol and pigment gallstones
- Cholesterol and bile acid metabolism
- Liver regeneration
- Liver transplantation
- Portal hypertension and varices
- Liver coma

Nutrition

- Nutritional requirements in health and disease
- Obesity
- Regulation of fuel mobilization and storage
- Exercise and energy metabolism
- Nutritional needs in disease
- Nutritional status assessment
- Dietary fiber
- Essential trace elements and minerals
- Nutrient transport, utilization, and function
- Special supportive nutrition in disease

DIVISION OF KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES

Renal Physiology and Pathophysiology

- Renal metabolism and transport
- Renin and hemodynamics
- Hypothalamic regulation of water balance
- Immunologic basis of renal disease
- Glomerulonephritis
- Interstitial nephritis
- Acute renal failure

Urologic Diseases

- Nephrolithiasis and urolithiasis
- Congenital anomalies of the urinary tract
- Bladder dysfunction
- Vesicoureteral reflux
- Urinary tract infection
- Prostatic hypertrophy
- Prostatitis

Chronic Renal Diseases

- End-stage renal disease
- Dialysis therapy
- Renal dialysis and its complications
- Kidney transplantation
- Nutrition and chronic renal disease

Hematologic Diseases

- Anemias of genetic origin
- Nutritional anemias
- Metabolic disorders of iron transport and storage
- Disorders of blood cell production
- Hematopoietic tissue transplantation immunology
- Autoimmune hematologic diseases
- Iron chelation therapy

Exhibit 1. NIDDK Research Areas: Some Representative Examples

Diseases	Prevalence (in millions)	Annual Economic Cost[1] (in billions)
Diabetes	11.0[4]	14.0[2]
Digestive Diseases	38.0	50.0[2]
Kidney and Urologic Diseases	13.0	5.5[3]

[1]Includes direct costs for hospital care, professional services, and drugs as well as indirect costs of productivity lost because of death and disability.

[2]As reported by the national commissions on diabetes and digestive diseases, respectively. In the case of digestive diseases, the National Digestive Diseases Advisory Board estimates an economic cost of $50 billion in annual lost wages, taxes, disability, and health care payments, and $17 billion in direct health care costs in addition.

[3]Direct medical cost of kidney disease only. (Source: National Kidney Foundation).

[4]Includes estimated number of undiagnosed cases in the population as well as the number diagnosed.

Exhibit 2. Prevalence and Economic Costs of Selected Disease Groups

STRATEGIES WITHIN THE MISSION

Historically, the concept of metabolism and metabolic diseases was a dominant theme in the overall scope of the Institute, and this has remained true to the present time. The closely related cluster of metabolism, nutrition, and endocrinology has provided a consistent focus of definition for the activities of the Institute, and these inevitably led to the study of immunological mechanisms underlying the diseases represented in Institute programs. The study of mechanisms has followed the needs of the research fields themselves, and has proceeded at all biological levels, molecular, cellular, tissue, organ, system, and organism in the environment.

The "common ground" of Institute concerns is illustrated in Exhibit 3, in which the significance of each of the four cluster components, metabolism, nutrition, endocrinology, and immunology, for each of the current NIDDK programs is shown. Current research approaches to the diseases for which the Institute has primary responsibility are almost uniformly multidisciplinary, and rely on this common ground of approaches, and involve skills and background knowledge from Institute programs other than the primary one. Examples are diabetes, cystic fibrosis, inborn errors of metabolism, malabsorption syndromes, obesity, kidney failure, benign prostatic hyperplasia, porphyrias, anemias, and many, many others. In each of these, research on the mechanisms of the disease and its complications spans the types of research under support by most of the Institute's programs.

There is another common thread which should be mentioned, inasmuch as it too contributes to the amount of mutual overlap of the Institute's programs. Not only do these programs represent the mechanisms and defects of metabolism and nutrition, they also include the major pathways of intake of nutrients and excretion of metabolic end products, as well as the hematologic transportation medium between, with its servicing of those major metabolic factories of enzyme systems and hormone messengers, the liver and the kidney. This range or scope of concerns allows an integrated overview of intake, processing, and output mechanisms and dysfunctions; within such a scope, research understandably benefits by collaborative efforts.

Reflecting these common or connected concerns, the Institute's programs attempt to facilitate interdisciplinary and collaborative efforts. The structure and operation of the Institute enable its leadership to put in place coordinated and integrated approaches which might be more difficult to accomplish across Institute lines. Some of the programmatic representations of this multidisciplinary perspective are shown as examples in Exhibit 3.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
SCIENTIFIC PROGRAM INTERACTIONS

Subject Interactions	Divisions: Diabetes, Endocrinology and Metabolic Diseases			Digestive Diseases and Nutrition		Kidney, Urologic and Hematologic Diseases		
	Diab.	Endocr.	Metab.	Digest.	Nutr.	Kidn.	Urol.	Hemat.
Metabolism (incl. Inborn Errors)	Major	Major	Major	Major	Major	Major	Major	Major
Nutrition	Major (esp. Type II)	Major	Major	Major	Major	Major	Import.	Major
Immunology (incl. Immunogenetics)	Major (esp. Type I)	Major	Import.	Major	Major	Major	Major	Major
Endocrinology (and Neuroendocr.)	Major	Major	Major	Major	Major	Major	Major	Major

Examples: (1) Obesity involves all subject areas above and all 3 Divisions
(2) Endocrine and exocrine relationships in the pancreas, and systemic effects

Program Interactions	Diabetes, Endocrinology and Metabolic Diseases			Digestive Diseases and Nutrition		Kidney, Urologic and Hematologic Diseases		
	Diab.	Endocr.	Metab.	Digest.	Nutr.	Kidn.	Urol.	Hemat.
Clinical Trials	X Diab. Clin. Trial					X		
Cooperative Programs	Kidney Dis. (Clin. Trial Proposed)				Diab.-related Nutr. Studies Obesity Studies	Diab. (Pima)		
Centers (Interdisc.)	X (DRTC's)	X (DERC's)		X (GI, Liver)	X (CNRU's, Obesity)	(X) (Under Consideration)	(X)	
Coop. in Epidemiology	X			X		X		
Data Bases and Clearinghouses	X			X	X	X		

Exhibit 3

II. NIDDK STRUCTURE AND OPERATIONS

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OVERVIEW

The Institute was established in 1950 through the Omnibus Medical Research Act and started its activities as the National Institute of Arthritis and Metabolic Diseases. In 1972 (Public Law 92-305), the name of the Institute was changed to the National Institute of Arthritis, Metabolic and Digestive Diseases, and in 1980 (Public Law 96-538), it became the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. The mission of the Institute and its scope of research have broadened significantly with the passage of time. In 1982, the Institute was designated a Bureau of the NIH, joining the National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Library of Medicine at that level. The Health Research Extension Act of 1985 (Public Law 99-158) divided the programs of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases into two separate institutes: the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

The organizational structure of the NIDDK (Exhibit 4) reflects the emphasis on basic biomedical and clinical research and research training. Institute efforts are planned and coordinated through both an extramural support program, which provides funding for research at universities, clinical facilities, and research institutions across the country and abroad, and an intramural component, which focuses on research conducted primarily within the NIDDK's laboratories and clinical facilities on the NIH campus and in Arizona.

The administrative and advisory activities of the Institute are organized to provide programmatic guidance and fiscal, analytical, and review services to facilitate the research effort. Activities aimed at developing and sustaining linkages to the scientific and health-care communities also fall within the Institute's realm of administrative and advisory functions.

OFFICE OF THE DIRECTOR

The focal point for managing NIDDK operations is the Office of the Director. Because this office has ultimate responsibility for the research sponsored and the results disseminated by the Institute, the Director and staff are involved in planning and coordinating the various activities of each of the NIDDK's programs.

Specifically, the Director's office provides policy direction and staff guidance and oversees the preparation of plans and reports in such areas as scientific program planning, administrative management, and use of resources. In addition, the Office of the Director is responsible directly for developing the NIDDK's annual budget, which reflects funding needs and resource priorities for program-related and administrative activities.

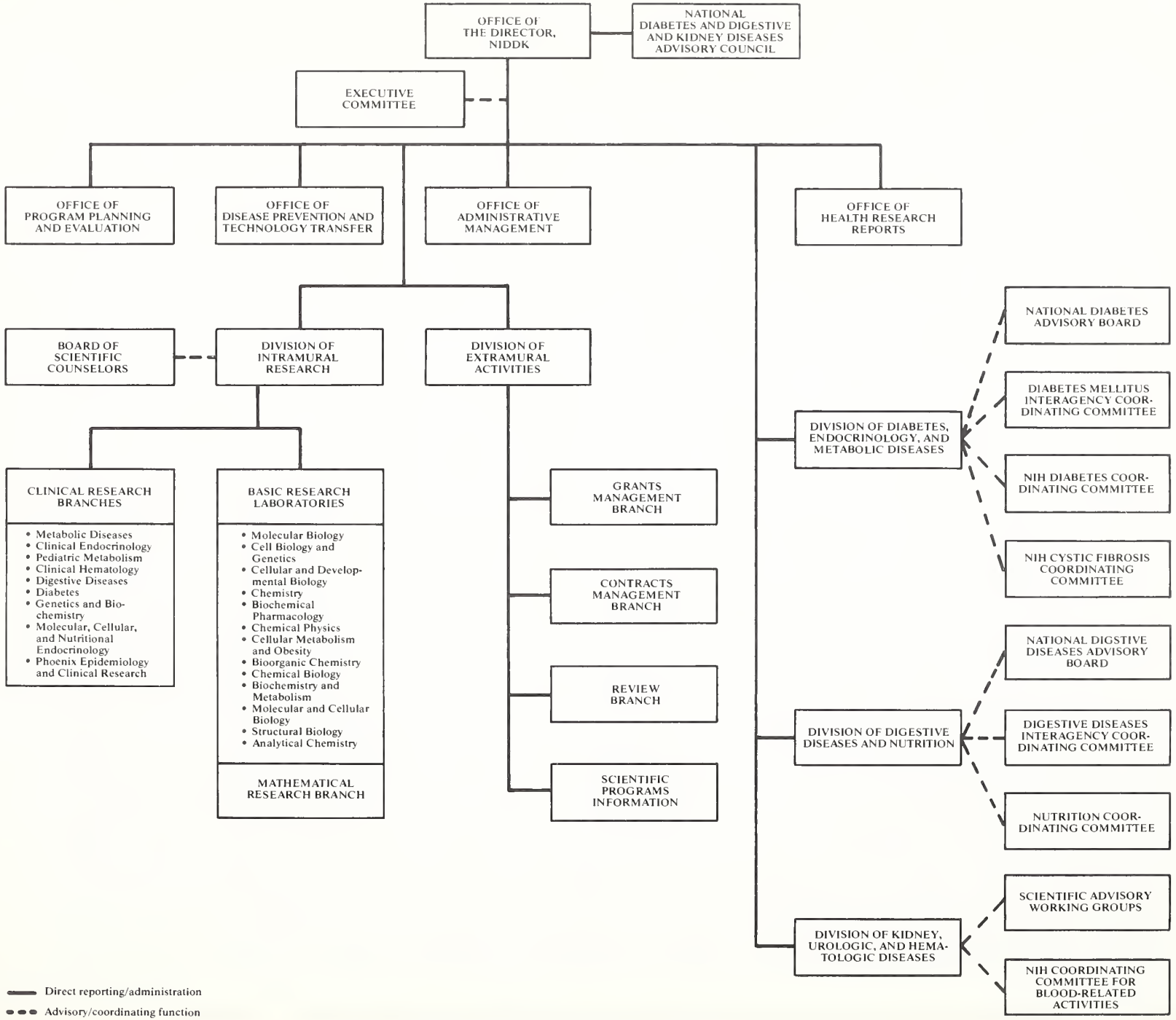

Exhibit 4. Organization of NIDDK

The Office of the Director coordinates and prepares information to describe the NIDDK's program progress and future plans to the Director of NIH and to Congress. These are ongoing activities that are mandated by the Institute's authorizing legislation so that progress achieved and problems encountered can be continually assessed.

The Office of the Director is assisted in its responsibilities by the following offices and program components:

- Office of Administrative Management--responsible for planning, coordinating, and directing management of day-to-day operations, including budget and financial management, personnel, and office services.

- Office of Program Planning and Evaluation--responsible for Institute activities in the areas of planning, program and policy analysis, evaluation, and legislation; analyzes Institute programs and develops Institute analytic capabilities and data base for planning, evaluation, policy formulation, and budget justifications; and oversees Institute Congressional activities having policy implications.

- Office of Disease Prevention and Technology Transfer--responsible for the Institute's programs in disease prevention, medical technology assessment and technology transfer, clinical trials, inventions and patents, orphan diseases and drugs, research animal matters, and Congressionally mandated periodic and ad hoc reports.

- Office of Health Research Reports--coordinates preparation and distribution of information and publications on the Institute's programs and activities to a variety of audiences, responds to public inquiries in areas relating to disease categories encompassed by the Institute's mission, and advises Institute staff on matters relating to the Freedom of Information Act.

- Extramural Divisions--provide oversight and management of all aspects of research and training programs and projects conducted off-campus as follows:

  --The extramural research Divisions coordinate and direct scientific planning, monitoring, and reporting of research and training programs in their respective research areas, in close cooperation with the Office of the Director.

  --The Division of Extramural Activities provides fiscal management of extramural research awards, reviews applications and proposals for specialized research projects, and assures operational coordination among the extramural research programs.

- Division of Intramural Research--through intramural laboratory and branch chiefs, plans, coordinates, and conducts research activities in the Institute's laboratories and clinical facilities.

These organizational components provide the substantive input that the Office of the Director requires to develop program plans and policies that are responsive to the Institute's long-term goals and objectives and to specific requests for information or studies originating in Congress or elsewhere in the Executive Branch. The Director's office also relies on the expertise and advice rovided by the National Diabetes and Digestive and Kidney Diseases Advisory Council, a senior consultative body whose guidance is important to the Institute's program operations and development, by the national advisory boards and coordinating groups described below, by a number of ad hoc committees of scientific experts, and by intramural and extramural senior staff members.

EXTRAMURAL ACTIVITIES

The extramural program supports investigations that are funded by the Institute but conducted at universities, private and public research facilities, and hospital-based clinical research centers throughout the Nation and, in certain cases, in other countries. The NIDDK uses grants, contracts, and various other funding mechanisms to generate and administer the extramural project activities of the research Divisions. The various award mechanisms are described in Exhibit 5. Because of its inherent advantages as a means of furthering scientific knowledge, the primary mechanism of research support used by NIDDK is the investigator-initiated research grant.

Each NIDDK Division functions as a distinct administrative unit with responsibility for allocating and managing research funds through research grants, contracts, fellowships, training grants, and special awards to qualified applicants and institutions. Supported activities range from basic and applied research investigations (including clinical studies) to training programs in fundamental and clinical sciences.

In keeping with the needs, priorities, and research requirements of the disease areas within the purview of the Institute, there is strong emphasis on the support of basic research. This emphasis is particularly important because the etiologies of many of the major diseases involved are unknown. At the same time, a significant proportion of extramural research support is directed at clinical studies, to provide an optimal mix for rapid advances in treating the various diseases and health problems studied by the NIDDK.

The testing for safety and efficacy of an emerging technique, drug, device, or procedure is generally accomplished through clinical studies and trials. Examples of such studies currently or recently supported include the following:

- Diabetes Control and Complications Trial
- Insulin infusion in Type 2 diabetes by implantable pump

Exhibit 5. NIDDK Extramural Program and Mechanism

- RESEARCH PROJECT GRANTS. An institution is awarded a grant on behalf of a principal investigator to facilitate pursuit of a scientific initiative or objective in the area of the investigator's interest and competence. Applications are accepted for health-related research and development in all areas within the scope of the Institute's mission. This is the largest single support mechanism utilized by NIDDK.

- PROGRAM PROJECT GRANTS. Program project grants are awarded to an institution on behalf of a principal investigator for the support of a broad-based, often multidisciplinary, long-term research program with a particular major objective or theme. The type of project supported with this award involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. Each project supported under a program project grant is expected to contribute to the overall program objective.

- CENTER GRANTS. Center grants are awarded to institutions on behalf of a program director and group of collaborating investigators to provide support for long-term, multidisciplinary programs of research and development; however, center grants are more likely to have a clinical orientation than are program project grants and are usually developed in response to announcements of specific program needs and requirements of the Institute.

- RESOURCE AWARDS. These awards provide support for research resources such as computer centers or general clinical research centers operating on an institutional, regional, or national basis. While the resources normally serve a wide range of biomedical research, they may be oriented toward specific research needs.

- CONFERENCE GRANTS. Conferences planned for the purposes of coordinating, exchanging, and disseminating scientific research information related to the Institute's program interests may be supported by conference grants. Generally, the awards are provided for cooperative participation with other organizations in the support of conferences rather than for provision of sole support.

- RESEARCH CONTRACTS. Contracts are offered for specific research problems that have been identified by the Institute and that require central direction, control, and management. Clinical trials of new or established therapies may be funded by this mechanism.

Exhibit 5. NIDDK Extramural Program and Mechanism
(Continued)

- DEVELOPMENT CONTRACTS. These contracts, which are relatively rarely used, are awarded for projects to produce substances, devices, systems, or other approaches to diagnose, prevent, treat, or control diseases. Examples of such projects include the development of effective vaccines or drugs, surgical techniques or medical devices to assist or replace organ functions, and sophisticated instruments to refine laboratory or clinical procedures.

- DEMONSTRATION CONTRACTS. These contracts are awarded to support projects designed to demonstrate the feasibility of applying biomedical research advances or technologies to individual or community situations to solve certain health problems.

- RESEARCH AND DEVELOPMENT SUPPORT. Awards in the research and development category are offered to finance certain resources or services to aid ongoing activities. These include data processing, drug testing, toxicology screening, logistics services, and collection and distribution of materials needed to conduct biomedical research and development.

- SCIENTIFIC COMMUNICATION AND EVALUATION AWARDS. These awards are provided to support special conferences, workshops, and seminars that are planned to analyze the significance of new biomedical research findings and for developing a scientific consensus on those findings.

- MANPOWER TRAINING AWARDS. A detailed description of the mechanisms used by the Institute to support manpower development is provided under "Research Manpower Development" in this chapter.

- EXPLORATORY GRANTS. These grants support planning for new programs, expansion or modification of existing resources, and feasibility studies to explore various approaches to the development of interdisciplinary programs that offer potential solutions to problems of special significance to the mission of the Institute. Such exploratory studies may lead to specialized or comprehensive centers.

- SMALL BUSINESS INNOVATION RESEARCH GRANTS. These grants support projects, limited in time and amount, to establish the technical merit and feasibility of research and development (R&D) ideas that ultimately may lead to commercial products or services. These awards may be made only to small businesses.

- Trial of ulcer hemorrhage with endoscopic hemostasis
- Endoscope, surgical, and drug therapy for bleeding varices
- Pediatric nephrology during trials and clinical surveys
- Study on plasmapheresis in severe lupus nephritis
- Medical versus surgical therapy of vesicoureteral reflux
- Renal transplant enhancement by donor-specific blood
- Studies of organ transplantation in animals and man
- Cooperative Clinical Study of the Effect of Dietary Modification on the Course of Progressive Renal Disease.

The Institute's extramural program funds and coordinates each trial over its full course, which may be several years. Population samples for a particular clinical trial may include several thousand people across the nation or a few hundred residents in a single community. Clinical trial results provide valuable information concerning the advisability of using the subject drug, device, or procedure in a health-care setting. They may also be useful in comparing the relative efficacy of two or more therapies for the same disease or health problem.

INTRAMURAL RESEARCH

The Division of Intramural Research conducts investigations at the Institute's laboratory and clinical facilities in Bethesda, Maryland, and Phoenix, Arizona. Intramural research activities are conducted by nine branches engaged primarily in clinical research on diabetes, metabolism, endocrinology, hematology, digestive diseases, and genetics; another branch is involved in the theoretical mathematical modeling of biological problems. In addition, there are 13 laboratories with component sections organized by scientific discipline (e.g., molecular biology, chemistry, pathology, pharmacology, physics, biochemistry, and others). The laboratories are engaged primarily in fundamental research that is related to the Institute's diverse areas of responsibility. The organization of the intramural laboratories and branches is shown in Exhibit 6.

A related intramural group, the Epidemiology and Clinical Research Branch, develops and applies epidemiologic methods in field studies among selected populations at risk for developing specific diseases. Investigators in the Epidemiology and Clinical Research Branch are located in Phoenix, but they also conduct research throughout the United States and provide assistance to numerous investigators engaged in research on diabetes and other metabolic disorders.

Monitoring and advice on intramural program direction and administrative activities are provided by the Board of Scientific Counselors, an external review committee. Close collaboration with scientists of other NIH Institutes,

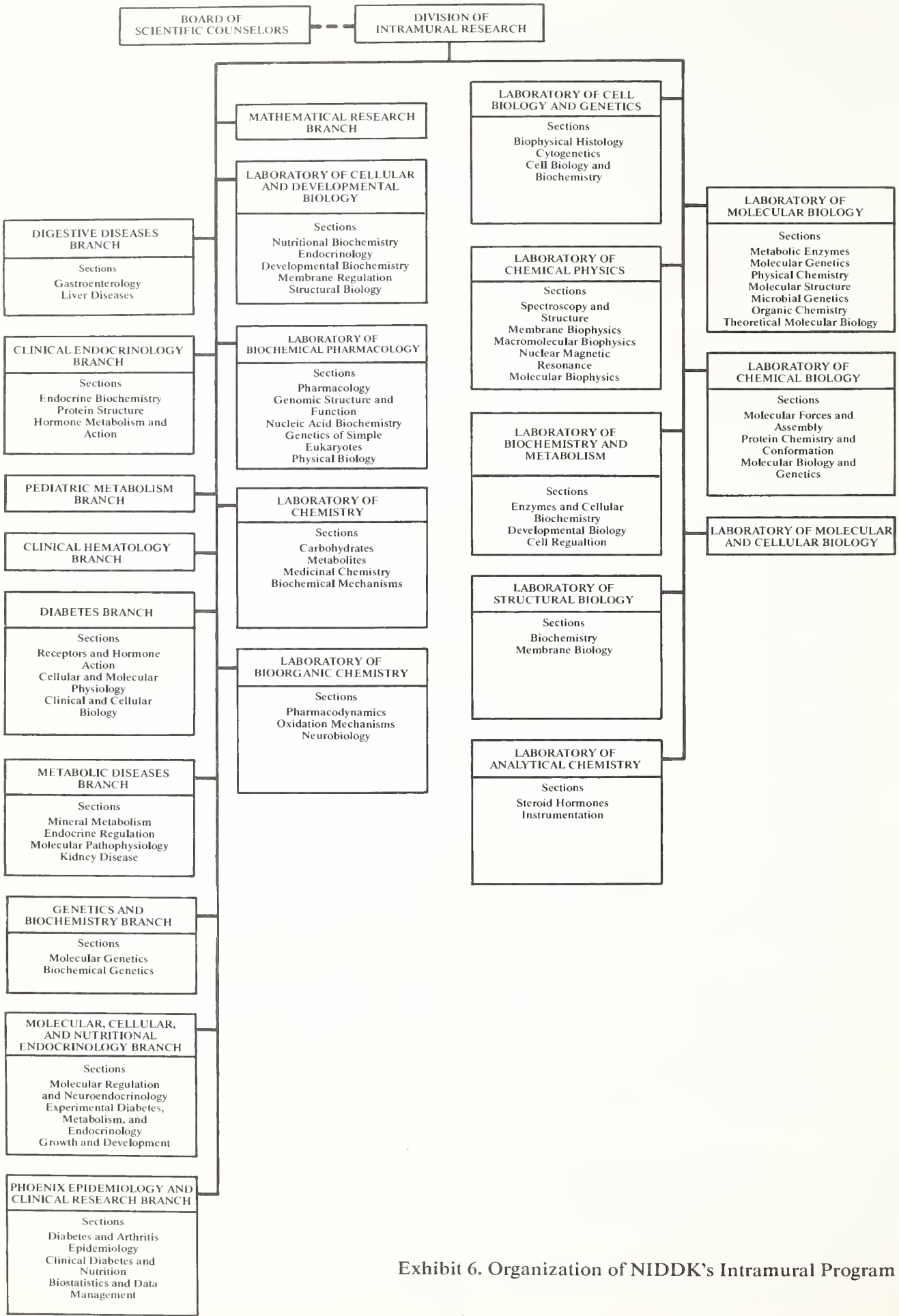

Exhibit 6. Organization of NIDDK's Intramural Program

other Government agencies, and investigators in institutions throughout the United States and abroad ensures an effective approach to research strategy. Moreover, because the intramural program constitutes such an important component of the NIDDK's activities and responsibilities, its ongoing and planned research efforts are given strong consideration in overall program planning by Institute management.

The intramural research staff of the NIDDK is generally acknowledged to be a highly productive and innovative group of scientists. The unusual caliber of this program is reflected in the several Nobel prizes and other prestigious awards that have resulted from its work. Also, many scientists who trained in the intramural research program of the Institute are now prominent faculty members at universities throughout the country. The various laboratories and clinical branches are universally sought after for scientific collaboration, while the mathematics branch serves as a major resource for the intramural efforts of the NIDDK and other NIH Institutes alike. The NIDDK is justly proud of the achievements and reputation of its intramural research program.

ADVISORY AND COORDINATING GROUPS

Over the years, the NIDDK's responsibilities and programs have been greatly influenced by the rapid evolution of biomedical research advances and technology, future research opportunities, and the public's demand for more and better health-care services. To keep pace with the rapidly developing biomedical research environment and to ensure that the NIDDK's numerous programs continue to address appropriately the Nation's health needs, the Institute relies heavily on guidance and recommendations provided by various advisory and coordinating groups. Each of these important bodies contributes to the direction, coordination, and evaluation of research and training activities in major disease areas.

National Advisory Council

The National Diabetes and Digestive and Kidney Diseases Advisory Council is one of the national advisory councils established legislatively for the NIH, each an important adjunct to its respective Institute. The NIDDK's National Advisory Council is composed of eminent experts in relevant areas of biomedical research; civic leaders, educators, and laypersons with interest in a particular disease or field of research in that disease; and representatives from the Department of Defense and the Veterans Administration.

The functions and responsibilities of the National Advisory Council are primarily to assist the Office of the Director in overseeing the activities of the Institute, provide advice and counsel with regard to the Institute's goals and programs, and review and approve or disapprove extramural research grant requests, after they have undergone a primary peer review for scientific merit and feasibility. The Council is charged with assuring that the extramural research projects supported by the NIDDK have a sound scientific basis, are relevant to the Institute's programs, and show promise of achieving results. The Council's involvement in the planning and coordination of programs within the Institute provides it with an appropriate perspective

for judging the merits of grant applications in light of the NIDDK's overall priorities for new research.

Members of the National Advisory Council are grouped into subcommittees, one for each of the three research Divisions that constitute the extramural research program. They are assigned to the subcommittee most appropriate to their special scientific, education, or public affairs expertise in a particular disease area. Each subcommittee is responsible for reviewing the substance of the extramural grant applications for research and training projects related to the diagnosis, prevention, and treatment of the diseases in its assigned area. Its recommendations on these research and training awards are then presented to the full Advisory Council for further consideration and final approval. The subcommittees also review and evaluate the overall administrative activities of their respective Divisions and suggest changes in program structure and operations when they deem such changes necessary.

National Advisory Boards

Among the many recommendations in the plans submitted by the national commissions on diabetes and digestive diseases was the establishment of national advisory boards for each disease area. When formally designated, each of these boards was authorized by Federal law to monitor and facilitate the research, training, prevention, and control programs within its area of interest.

The National Diabetes Advisory Board (NDAB) and National Digestive Diseases Advisory Board (NDDAB) are composed of members representing a variety of scientific, educational, health-care, and public-service disciplines. Current members of the boards are listed on the following pages.

The primary functions of each board are to review and evaluate progress of the long-range plan developed for its respective disease area; update the plan to assure its continuing relevance to public health needs; provide advice and recommendations on plan implementation to the Directors of the NIDDK and the NIH, the Secretary of Health and Human Services (HHS), and other Federal agencies; and maintain liaison with advisory bodies of other Federal agencies involved in implementing the plans.

To keep Congress informed of all ongoing activities, issues, and anticipated needs in their disease areas, the advisory boards are required by law to submit annual reports of their activities along with recommendations for any appropriate changes in the plans.

Interagency Coordinating Committees

The NIDDK fulfills the mandate for interagency cooperation through two interagency coordinating committees, which are specifically responsible for fostering and improving research and health-care programs in the areas of diabetes mellitus and digestive diseases. These committees, which were created as a result of Congressional acts, serve to facilitate communications among all Federal agencies directly or indirectly involved in the three

disease areas. From their establishment in the mid-1970s, the committees worked closely with the national commissions and advisory boards to develop improved approaches to information exchange, joint planning, and the identification of promising areas for cooperation.

The membership of each interagency coordinating committee includes the director of the applicable NIDDK Division, who serves as chairman, and representatives from selected Institutes within the NIH and from other Federal departments and agencies with related functions and activities. Through these committees, the Institute is able to determine whether programs of research, health care, and related social services are adequate to meet the needs of those suffering from diabetes and digestive diseases.

Trans-NIH Coordinating Committees

Certain complex health issues or problems span the program interests of several Institutes, thereby requiring collaborative effort to assure program balance and to minimize duplication of activity. For such trans-NIH issues, the Director of the NIH has appointed coordinating committees to provide a forum for exchange of information, a mechanism for the coordination of individual programs, and a focus for policy development. The coordinating committees are composed of representatives of all the appropriate Bureaus, Institutes, and Divisions (BIDs) within the NIH. Their activities foster the continuing development of new research approaches in the participating NIH components, and the committee chairman serves as a principal advisor to and representative of the Director, NIH, on all matters relating to that area. The following sections describe coordination efforts in several trans-NIH areas in which the NIDDK plays a major role.

Diabetes. Because diabetes affects so many body systems, research programs in this area fall within the scope of almost all of the BIDs. Thus, the Trans-NIH Diabetes Research Program was established to promote cooperation in diabetes-related programs among all of the relevant Institutes at the NIH. Activities have included joint program announcements and requests for applications as well as cooperation in fostering research manpower development programs.

Participants in the trans-NIH diabetes program also collaborate with the NIDDK's National Diabetes Data Group. The data group serves as the central point within the NIH for the collection, analysis, and evaluation of epidemiological data that are fundamental to the development of sound scientific and public health policies related to diabetes and its complications. Members of the trans-NIH diabetes program also utilize the NIDDK's National Diabetes Information Clearinghouse, the national reference source for information on professional and patient education materials and programs related to diabetes and its complications.

Nutrition. The NIH is the primary Federal agency that conducts and sponsors research and training in nutrition related to health maintenance, human development, and disease prevention and treatment. The NIH Nutrition Research Program involves all of the BIDs at NIH that support nutrition-related research and is coordinated through the Nutrition Coordinating

Committee (NCC). The NCC not only minimizes duplication of effort among the NIH components but also identifies areas in which research and research manpower in nutrition require further development. Program announcements and requests for grant applications made by the NCC and sponsored by more than one BID encourage activity in areas of perceived need in nutrition.

The NCC has developed a master nutrition plan and prepares an annual report entitled Program in Biomedical and Behavioral Nutrition Research and Training that emphasizes research in four critical areas: clinical nutrition throughout the life cycle, the role of nutrition in disease development, prevention of disease, and treatment of disease. In addition to identifying research priorities, the nutrition plan emphasizes the transfer of modern nutrition technology and nutrition education for professionals and the public.

The NIDDK's involvement in the NCC has included the full range of NCC activities but has focused particularly on several of immediate Institute concern: evaluation of the clinical nutrition research units, with the National Cancer Institute; preparation of a program announcement on overnutrition and obesity, with seven NIH Institutes; participation on a planning committee on problem areas in the support of nutrition work; and preparation of data, analyses, and textual information concerning the NIDDK programs in specific areas of nutrition.

Cystic Fibrosis. The Cystic Fibrosis Coordinating Committee was established to serve as a focus for the coordination of NIH support of research and research training related to cystic fibrosis (CF). The committee is cochaired by representatives of the NIDDK and the National Heart, Lung, and Blood Institute (NHLBI) and includes members from each of those BIDs with responsibilities relating to CF. Specific functions of the committee include cataloguing NIH activities and support related to CF, coordinating and facilitating program initiatives in the BIDs to address the needs and opportunities in research relevant to CF, encouraging trans-NIH collaboration on activities related to CF, and serving as an information resource and point of contact with other agencies and organizations regarding advances and opportunities in CF research and research training.

Blood-related Activities. Support and management of blood-related research activities are shared among several Institutes of the NIH. The NIH Coordinating Committee for Blood-Related Activities coordinates the overall course of investigations dealing with blood and the use of blood resources. The membership of the coordinating committee represents six Institutes at the NIH, including the NIDDK, the Division of Research Resources, and the NIH Clinical Center. One of the major goals of the committee is to exchange information on proposed initiatives related to blood to ensure the best possible focus of activities.

Board of Scientific Counselors

The NIDDK's Board of Scientific Counselors was initiated in 1956 and currently operates under the statutory authority of Section 222 of the Public Health Service Act (P.L. 87-838, Public Health Service Amendments of 1962), serving as an internal review committee responsible for monitoring the activities

of the Institute's intramural research program. The operations of the Board are governed by the Federal Advisory Committee Act, P.L. 92-463. The formation of the Board was considered essential to ensure unbiased, extra-Governmental expert review of intramural research activities. The activities of the Board developed in parallel with the review mechanisms established for the extramural research program.

The Board is composed of individuals eminent in research fields and scientific disciplines related to the basic and clinical research activities of the Institute. Board members, listed below, meet twice a year to visit Institute laboratory facilities, review scientific progress, and make recommendations for the program to the Director of the Division of Intramural Research, the Director of the NIDDK, and the Director of the NIH. In addition, the Board is required to submit an annual report on findings to the Secretary, HHS, the Assistant Secretary for Health, and the Director, NIH.

SPECIAL PROGRAMS

Because of the NIDDK's varied responsibilities, there are many opportunities for fostering collaboration among scientists across the nation and around the world. Over the years, the Institute has implemented special programs to expand research opportunities and services, going beyond the laboratory into the community where those affected by disease and those who treat them may benefit more quickly from research progress.

NIDDK's Research Centers Programs

In addition to providing support to institutions and organizations for the traditional research and research training programs, the Institute also has responsibility for a program of center facilities. Through the centers programs, some of which were specifically authorized by legislation in the mid-1970s, institutions have been competitively selected to provide a variety of multidisciplinary approaches to research, education, and community demonstrations in diabetes, endocrine and metabolic disorders, and digestive diseases and nutrition-related problems.

The Diabetes Centers Program consists of two types of facilities: diabetes-endocrinology research centers (DERCs), which concentrate on basic and clinical investigations conducted in a core setting of shared comprehensive laboratory facilities, and the diabetes research and training centers (DRTCs), which encompass basic and clinical research as well as the education and training of new investigators and the translation of research results into improved care and management of diabetic patients. For added research incentive, both DERCs and DRTCs provide limited funds for pilot or feasibility studies to encourage young investigators and promote innovation in research concepts.

The Division of Digestive Diseases and Nutrition sponsors centers that support and conduct basic and clinical investigations in a variety of health problems related to its program areas. Three such centers conduct research on liver disease and the effects of drugs and injuries on the liver. Another center is studying diet and eating behavior that contributes to obesity, a

model program that is intended to foster multidisciplinary research and exchange of information. Still another focuses on peptic ulcer, and five new centers focus on studies of gastrointestinal physiology, neurophysiology, and endocrinology.

The Institute also is supporting five clinical nutritional research units, which serve as focal points for multidisciplinary research in clinical nutrition as well as provide for the development of programs in clinical nutrition that enhance the education of various health professionals.

Activities of the various types of centers differ according to local need and support of research, clinical, educational, training, and demonstration projects. All centers, however, operate in a core setting of shared, comprehensive facilities, resources, and trained investigators to promote research and the translation of research results into improved patient care.

The multipurpose centers program provides important linkages among the NIDDK, the scientific community, and the health care delivery system; continued evaluation is essential to maintaining those linkages.

A Program for International Cooperation

The NIDDK supports a number of international collaborative and individual research efforts that draw upon the talents and investigative expertise of the international scientific community. Continued collaboration with international scientists and the funding of research projects that may have worldwide impact is an ongoing priority for the Institute. Through the Bilateral Cooperative Agreements Program, the NIDDK has developed collaborative and cooperative activities with other countries in several important fields.

U.S.-Japan Cooperative Program in Malnutrition. Since 1966, the U.S.-Japan Cooperative Medical Sciences Program has been actively engaged in collaborative research efforts to develop greater understanding of the effects of malnutrition on physical growth, mental development, and performance. More recently, emphasis is on nutritional aspects of bone disease, nutritional assessment, nutritional significance of unsaturated fatty acids and sulfur-containing amino acids. These activities and projects are carried out through cooperative arrangements developed between the United States and Japan, which share responsibility for the program.

Research continues to be the primary focus of activities supported by the malnutrition program panel. Studies have been developed and conducted abroad among populations with nutritional deficiency diseases and are designed to find solutions to complex malnutrition problems. The availability of large population groups afflicted with nutrition disorders provides the NIDDK and the other sponsoring members of this program with valuable information and insight into the many aspects of nutrition and malnutrition and their implications for health and well-being.

India. A 5-year agreement between the Tata Institute of Fundamental Research, Bombay, and the NIDDK Laboratory of Molecular Biology on a study, "Conformational Structure of Polynucleotides, Nucleotides, and Nucleosides," continues.

Spain. Under the U.S.-Spain Joint Committee for Scientific and Technological Cooperation, it was agreed that a Health and Diabetes/Fetal Development study would be undertaken on the topic, Insulin, Its Effects and Risks During Embryonic Development. This will be undertaken in collaboration with the Autonomous University, Barcelona, and the Diabetes Branch, NIDDK.

Yugoslavia. Under the U.S.-Yugoslavia Scientific and Technical Cooperation Projects Program, two studies continue in collaboration with the NIDDK Laboratory of Chemical Physics: a study of gas phase electronic structure of small molecules and their radical cations and, in collaboration with the Clinical Hematology Branch, a study on measurement of young platelets with cytochemical methods.

U.S.-Israel Binational Foundation. Several NIDDK intramural scientists collaborate with Israeli scientists and serve in an advisory capacity to the the foundation. Some of the studies include:

- Structure and function of the tetanus toxoid receptor and the mode of disease action;
- Secretion of insulin from diabetic and nondiabetic pancreatic islets;
- Endothelial specificity in endocrine tissues; and
- Nucleosome and higher order chromatin structure, interactions, and structural transitions.

Visiting Scientists Program. The NIDDK intramural research program sponsors researchers from many countries under its visiting scientists program, and in return, intramural investigators from the Institute visit and collaborate with scientists in laboratories and clinics abroad. During the past year, researchers from Israel, India, Poland, Japan, China, the United Kingdom, France, Germany, Italy, and other countries have worked in the intramural laboratories and clinics of the NIDDK. The exchange of high-caliber scientists across national boundaries promotes cross-fertilization of ideas and techniques; it has proven mutually beneficial for many years and is expected to continue to provide significant scientific dividends in the future.

Extramural Research in Other Countries. To capitalize on the expertise of investigators in other countries and to further the progress of research in high-priority health problems of international scope, the NIDDK supports investigator-initiated research by scientists outside the United States as part of its extramural research programs. Support is provided through grants and occasionally contracts for highly qualified investigators conducting the following types of studies:

- Diabetes in the Pacific--genetic and environmental interactions
- Pairing of insulin chains during laboratory synthesis

- Impact of feedback techniques on clinical course of diabetes
- Relationship of glucose control and early vascular complications of Type 1 diabetes
- Inborn errors of carbohydrate and lipid metabolism
- Mechanisms of oxygen storage and transport in red blood cells
- Behavior of unipolar MDCK cells in culture
- The role of the ubiquitin conjugation pathway in intracellular protein breakdown
- The genetics of steroid hydroxylation
- Neurotransmitter receptors and the adenylate cyclase second messenger system
- Structure and function of thyroglobulin
- Effect of thyroid-stimulating hormone on thyroid gland cells
- Deleterious effects of certain toxins and drugs on hepatocytes
- Molecular basis of secretion in the exocrine pancreas
- The effect of gut peptides on the central nervous system
- Immunosuppressive drugs for renal transplantation
- Long-term effects of continuous ambulatory peritoneal dialysis
- Studies on hereditary hemoglobinopathies
- Clinical studies of Pentoxyfilline in thalassemia.

Conferences, Seminars, and Meetings. Scientific meetings with international audiences play a major role in scientific communication because they provide a forum for the exchange of research information among investigators from different countries, and they often stimulate further scientific collaboration. The NIDDK supports selected international conferences and symposia as part of its programs; for example, last year the NIDDK provided support to six such meetings that addressed topics such as molecular biology, immunology, hormones, diabetes, hematology, dialysis, renal transplantation, kidney stones, and basic science.

RESEARCH MANPOWER DEVELOPMENT

In the 35 years since its establishment, the NIDDK has made impressive strides in biomedical research. Maintaining that momentum requires a complex interplay of factors, including the availability of basic scientific knowledge and technologic methods, the availability and appropriate utilization of trained investigators, and financial support. While the lack of any single resource may impede scientific progress, the need for trained personnel is particularly critical. The development of research manpower is crucial to the accomplishment of the NIDDK's goals and has been a high Institute priority.

Through ongoing analysis and evaluation of program needs and maintenance of a wide range of training mechanisms, the NIDDK continues to seek motivated future investigators to meet critical needs. Relatively recently initiated training mechanisms, such as the Clinical Investigator Award and the National Research Service Award Senior Postdoctoral Fellowship, as well as the New Investigator Research Award, contribute markedly to Institute efforts to attract and prepare outstanding investigators for research careers. The Physician Scientist Award (see below) is expected to provide one of the most effective mechanisms available to help reach this goal. Exhibit 7 describes the mechanisms used by the NIDDK to supply talented scientists for each of its categorical disease research programs.

Vigorous efforts have been made to avert shortages of personnel in vital areas. However, there are still declining numbers of physicians who pursue research careers and a shortage of trained epidemiologists in many important fields.

Physician Researchers

In an effort to attract more physicians to academic research careers, the NIDDK promotes short-term training programs for students in professional schools. During summer breaks, students are given the opportunity to gain research experience and be exposed to the rewards of a research career at a formative stage of their professional training. Once they have received their professional degrees, such students are eligible for grants in individual or institutional postdoctoral training programs, and those with demonstrated dedication and aptitude in research are eligible for the Clinical Investigator Award, the Research Career Development Award, and the Physician Scientist Award. By continuing to support physicians throughout the various stages of lengthy research training, the NIDDK can help to ensure that adequate numbers of physician researchers will be available to address the Institute's research concerns from both basic and clinical perspectives.

Other Research Professionals

Often, critical manpower needs arise in specific areas or disciplines. For example, progress in epidemiologic studies has been restricted severely because the number of professionals trained in pertinent fields is insufficient. To correct this deficiency, the NIDDK encourages the formal training of epidemiologists in field and survey methods through university-based

Exhibit 7. NIDDK Research Manpower Development Mechanisms

- NATIONAL RESEARCH SERVICE AWARDS (NRSA). These awards provide for the training of biomedical and behavioral scientists in areas of national need. Awards can be in the form of individual postdoctoral fellowships or institutional training grants. After completing NRSA-supported training, recipients are usually expected to engage in biomedical or behavioral research or teaching for a period equal to the period of support.

  --Individual postdoctoral fellowships. Individual NRSAs are made to applicants who have received a Ph.D., M.D., or equivalent degree for postdoctoral research training. The award provides the opportunity to carry out supervised research so that biomedical scientists, clinicians, and others can broaden their scientific backgounds and expand their potential for research in health-related areas. Each applicant must have arranged to work with a sponsor affiliated with an institution having the staff and facilities needed for the proposed training. Federal laboratories such as those of the NIDDK's intramural programs and universities, medical schools, research hospitals, and similar public or private institutions are among the eligible organizations. Recipients are selected through national competition.

  --Institutional training grants. An institutional NRSA may be awarded to a domestic public, nonprofit private, or Federal institution to support a training program in a specific area of research. In most instances, institutions may request support for both pre- and postdoctoral trainees. The applicant institution must have or be able to develop the staff and facilities required for the proposed program and is responsible for selecting trainees. Predoctoral trainees must have received an appropriate baccalaureate degree, and individuals at the postdoctoral level must have received a Ph.D., M.D., D.D.S., D.V.M., or equivalent degree. Institutional grants are for periods of up to 5 years and may be renewed; however, no individual may receive more than 8 years of support (5 years predoctoral, 3 years postdoctoral) unless a waiver is granted by the NIDDK.

  --Short-term training for students in professional schools. The NIH has initiated a program to provide research experience for talented students in professional schools. The program is designed to help avert a shortage of clinical investigators by attracting highly qualified professional students to careers in biomedical and behavioral research. Domestic schools of medicine, osteopathy, dentistry, veterinary medicine, optometry, pharmacy, and podiatry may apply for grants to support short-term research training for their students for discrete periods of up to 3 months.

Exhibit 7. NIDDK Research Manpower Development Mechanisms
(Continued)

--Senior postdoctoral fellowship. Investigators who have held the doctorate for at least 7 years may apply for a senior postdoctoral fellowship. These awards are intended to provide more established investigators with the opportunity to broaden their scientific background and expertise in health-related research. A senior postdoctoral fellowship is usually awarded for 1 year, is subject to NRSA payback requirements, and may not exceed 3 years' total support unless a waiver is granted.

- CLINICAL INVESTIGATOR AWARD (CIA). The CIA is directed to clinically trained individuals with demonstrated aptitude in research and provides them the opportunity to develop into independent biomedical investigators. Offering salary support as well as fringe benefits, the CIA program specifically seeks to develop research ability in individuals with clinical background and training. This award is intended to provide research support in the transition between fellowship or trainee experience and a career in independent investigation.

- RESEARCH CAREER DEVELOPMENT AWARD (RCDA). The RCDA is a special grant awarded to an institution for support of a named individual. It provides salary and fringe benefits for 5 years so that the awardee may be relieved of teaching and administrative duties and pursue research interests full time. The program's goal is to provide opportunities for the enhancement of the research capabilities of individuals in the formative stages of their careers who have demonstrated outstanding potential for contributing as independent investigators to health-related research. The awards are available for persons whose research potential is apparent but who need additional experience in a productive scientific environment.

- PHYSICIAN SCIENTIST AWARD (PSA). The PSA is a new award intended to encourage newly trained clinicians to develop independent research skills and experience in fundamental science and basic biomedical disciplines. It is a 5-year nonrenewable award based on up to five consecutive full-time 12-month appointments. Eligibility is restricted to those holding health professional degrees in the clinical sciences (M.D., D.D.S., D.V.M., D.O., or equivalent). Physicians also holding the Ph.D. are ineligible. Candidates ordinarily will have completed at least 1 postgraduate year of clinical training by the time the award is made. Each candidate must identify a primary sponsor who is recognized as an accomplished investigator in the basic science research area proposed and who will provide guidance for the awardee's development and research plan. The awardee's program is designed in two phases. In phase I, there is a basic science learning experience that culminates, in phase II, in an intensive research activity under the general guidance of the sponsor.

Exhibit 7. NIDDK Research Manpower Development Mechanisms
(Continued)

- NEW INVESTIGATOR RESEARCH AWARD (NIRA). To help bridge the transition from training status to that of established investigator, this award provides funds for relatively inexperienced investigators with meritorious research ideas. The award is designed to encourage the development of research interests and capabilities among both new investigators and those who interrupted their early promising research careers. This special program provides 3 years of nonrenewable research grant support for the initial independent research efforts of new investigators.

degree programs, nondegree programs in the diabetes centers, and epidemiologic projects at the Centers for Disease Control, the National Center for Health Statistics, the Veterans Administration, and the field studies units. Recognizing the importance of epidemiologic studies to comprehensive national research efforts, the NIDDK established an arthritis epidemiology program office in 1978 to encourage research in rheumatic diseases and, with seven other Institutes, solicited applications for diabetes epidemiology research and training. By marshalling all available resources and coordinating them efficiently, the NIDDK hopes to moderate or avert the severe shortages of trained personnel anticipated in coming years.

Minority Program Support

Traditionally, ethnic and racial minorities and women have been underrepresented in the mainstream of biomedical research, but the Nation cannot afford to allow such human resources to remain untapped. Therefore, the NIDDK vigorously supports programs to strengthen research capabilities and enlarge the potential investigator pool in colleges and universities attended largely by women and minority groups.

In 1977, the NIDDK participated in the initiation of the NIH Extramural Associates Program to familiarize minority and women's educational institutions with NIH research activities, thus enhancing their capabilities to participate in NIH-supported health research. Through the Minority Biomedical Research Support Program of the Division of Research Resources, the NIDDK funds projects designed to improve the biomedical science capabilities of minority institutions through support of undergraduate and postdoctoral students and staff and faculty positions. Currently, the NIDDK is committed to a level of support of approximately $1.60 million each year.

The Minority Access to Research Careers Program intra-agency agreement with the National Institute of General Medical Sciences enables the NIDDK to increase the number of minority biomedical researchers by making funds available for predoctoral faculty fellowships, visiting scientists, and honors undergraduate training. This agreement is in the process of being renewed.

Scientists from the NIDDK visit minority institutions, giving scientific lectures and advising students on careers in biomedical sciences. In addition, the Institute's Equal Employment Opportunity Office distributes scientific journals and scientific textbooks contributed by staff scientists to minority colleges and universities and participates in the Black Colleges Initiative, originated by Executive Order in 1980 to overcome the effects of discriminatory treatment and to strengthen the ability of historically black colleges to provide quality education and participate in Federally sponsored programs.

DISEASE PREVENTION

In recent years, prompted in part by encouraging developments in the science base and in part by the increasing cost of health care, the Nation has placed greater emphasis on finding ways to reduce the toll of disease. One way in which the Department of Health and Human Services participates in

this goal is through its initiative on disease prevention and health promotion. Modern prevention research has increased in complexity because of the shift in the relative prevalence of such chronic diseases as diabetes when compared with acute infectious diseases such as pneumonia and tuberculosis, which were more common at the beginning of the century. The concerns of disease prevention and health promotion among the American people thus have become more challenging to research scientists throughout the country.

The NIDDK has long been involved in prevention-related research, although such activities may not always be labeled as such. The primary product of the Institute is knowledge, the ultimate aim of which is prevention, because prevention of disease clearly is the most useful extension of knowledge in the health field. At the NIDDK, prevention research has as its objectives both the protection of people from disease and the prevention of the progression of disease to disability or early death.

Focus of NIDDK Prevention Research

Many diseases under study at the NIDDK have yielded to basic research, and scientists are now designing means of prevention that will be translated into health care practice, if they are shown to be safe, effective, and feasible. Many of the projects described in this report have important implications for disease prevention and health promotion, and major examples of ongoing prevention research activities for each NIDDK Division are highlighted below:

- Prevention of the emergence and progression of Type 2, or non-insulin-dependent (formerly maturity-onset) diabetes in individuals with an inherited tendency for this disorder

- Prevention of the appearance and progression of the clinical complications of Type 1 (formerly juvenile-onset) or insulin-dependent diabetes

- Prevention of dwarfism and normal-variant-extreme short stature

- Prevention of the recurrence of peptic ulcer in patients with a known history of the disorder

- Prevention of obesity and its many detrimental effects on health

- Prevention of the recurrence of kidney stones and their sequelae in known stone-forming patients.

Future Prevention Research

In addition to the continuing studies noted above (and many others), several other major areas of investigation offer promise for future accomplishments in prevention, for example:

- Research on the factors that predispose older men to the development of benign prostatic hyperplasia, with the goal of eventual prevention or amelioration of this widespread disorder

- Research on prevention and better control of diverticulosis (protrusion of portions of the inner lining of the gut through weak spots in the circular muscles of the lower intestine) and diverticulitis (infection and inflammation of these intestinal herniations) in the aged through lifelong adequate supply of dietary fiber (bulky roughage).

Prevention Education and Outreach

Several NIDDK programs that relate to prevention feature interaction with the scientific and public health communities, health providers, and consumers. These programs are described in other sections of this report. Major activities are as follows:

- Diabetes Research and Training Centers

- Clearinghouses

- Clinical nutrition research units

- Special activities.

As insights into the causes and development of chronic diseases are developed, new strategies for preventing the onset or destructive progression of these diseases are devised. However, it is clear that modification of habits and lifestyles--such as avoidance of obesity, dietary changes, and adequate physical exercise--will have an important influence on the degree of success achieved by many of the Institute's prevention initiatives. In light of the man-made risk factors in so many disease categories, successful prevention will depend not only on biomedical advances but also on current advances in educational, social, and legislative approaches to encouraging behavior change.

TECHNOLOGY ASSESSMENT AND TRANSFER

Before the scientific revolution of the 1800s, physicians practiced medicine more as an art than a science. With the rapid technologic strides of the last 50 to 75 years, however, the relative advantages of newer methods, devices, and procedures have been identified; innovations have been more readily accepted and adopted; and the discipline of medicine has moved toward the practice of technology-based science.

Determining Research Impact on Health Care

Technology assessment, a form of policy research that examines short- and long-term consequences of the use of technology, is an essential safeguard of the public's right to safe and effective health care. Medical technology assessment is concerned not only with scientific and medical aspects of advances in diagnosis, treatment, and prevention of disease but also with indirect, delayed, or unintended social impacts of medical innovation, and, in consideration of economic realities, it vigorously examines and determines the optimal balance among the benefits, risks, and costs of health technologies.

The Office of Disease Prevention and Technology Transfer is the focal point for assessing medical technologies conceived, tested, and evaluated in NIDDK programs and for advising the Public Health Service and other agencies. Technology assessment activities of the NIDDK include workshops, symposia, and consensus conferences to synthesize expert opinion; state-of-the-art reviews of issues within the NIDDK research purview to assist the Public Health Service in the assessment of health technologies; and evaluation of inventions developed in extramural and intramural research.

Utilizing extensive surveys of the most recent scientific literature and input from Institute experts and other scientific consultants, the NIDDK provides assessment of medical and surgical procedures and treatments and advice to the Health Care Financing Administration concerning Medicare coverage for medical, surgical, and diagnostic technologies. Examples of technologies that have been assessed during the last year include:

- Nuclear magnetic resonance imaging
- Twenty-four-hour ambulatory esophageal pH monitoring
- Antigastroesophageal reflux implantation device
- Apheresis for the treatment of systemic diseases
- Percutaneous transluminal angioplasty for failing arteriovenous dialysis fistulas.

Consensus Development Conferences

In addition to participating in approximately 50 national and international scientific conferences, workshops, and seminars each year, the NIDDK takes part in the NIH consensus development program, by which various concerned parties are brought together to seek general agreement on a particular health issue or on the safety, efficacy, and appropriate conditions for use of a particular medical technology.

During the last year, the NIDDK organized, in conjunction with the NIH Office of Medical Applications of Research and the National Heart, Lung, and Blood Institute, a consensus development conference on "Health Implications of Obesity." Since the subject matter constitutes an important and growing public health problem in the United States as well as in other industrialized

countries, experts form Western Europe participated in the program, and interested scientists from throughout the world attended the conference. It was the largest NIH consensus conference organized in Bethesda thus far. The topic was a particularly timely one, and the resulting statement of findings and recommendations of the consensus panel attracted considerable attention in the medical literature and among the attending medical practitioners. The mass media of communication gave the conference an unusually heavy emphasis and featured the consensus statement's conclusions for weeks and months after the meeting. The consensus statement was broadly distributed to the medical profession. The proceedings of the conference and text of the consensus statement were subsequently published in toto by Annals of Internal Medicine, the journal of the American College of Physicians.

Technology Transfer

The NIDDK recognizes that unless the technologic knowledge gained in basic and clinical research is diffused for application in the health care community, the full value of that research will not be realized. Therefore, the Institute devotes significant effort to systems that foster transmission of the latest scientific knowledge and techniques to this community.

The goals of technology transfer are to increase awareness and interest in new research advances, to promote scrutiny and evaluation of their potential advantages, and to foster their trial and adoption in practice. The NIDDK serves a range of constituency groups that includes basic and clinical researchers, health-care practitioners, voluntary and other health agencies, medical educators, and the public. Their individual needs for information are different and may vary at different stages of technologic evolution. Because no single network for information dissemination can satisfy the full spectrum of information needs, the Institute uses various means to promote information diffusion and technology transfer:

- Information collection and dissemination. The NIDDK's Office of Health Research Reports is the focal point for an integrated program of information collection and dissemination of research highlights, program achievements, and disease-related materials. The office is responsible for coordinating the production and distribution of publications concerning Institute activities; answering inquiries from Congress, the White House, the media, and the public on NIDDK activities and disease-related information; providing advice to scientific and program staff engaged in research reporting; and cooperating with voluntary and professional health agencies in the coordination and planning of publications and reports of clinical and research activities.

- Clearinghouses. Important components of the Institute's information program are the National Diabetes Information Clearinghouse and the National Digestive Diseases Education and Information Clearinghouse. Their primary objective is to bridge the communication gaps between those who are developing knowledge through research, those who suffer from the

effects of these disorders, and those who direct their care. To this end, the clearinghouses have evolved as national centers for compiling educational materials and information available from various sources, ranging from technical information manuals for health professionals to audiovisual presentations developed especially for elementary-school children. In serving as brokers to facilitate the flow of information, the clearinghouses maintain data bases cataloguing thousands of brochures, booklets, reports, journal articles, textbooks, and audiovisual materials and refer clients to appropriate developers or sources, rather than act as distributors of printed matter.

- Diabetes Research and Training Centers. These centers have education and demonstration components with information, continuing education, and training programs for medical and allied health professionals and for patients. Of particular importance are programs of education and information dissemination for the general public concerning new technologies and discouragement of the use of unapproved and ineffective treatment measures.

- Scientific Conferences. Members of the scientific and medical community, as potential adopters of new technologies, vary widely in their receptiveness to newly communicated innovations. While some investigators and practitioners make particular use of impersonal sources such as printed materials to learn about new information, many tend to rely on personal interchange and the experiences of their peer group. Though wider audiences can be reached by journals and textbooks, the information provided by these means is often not sufficiently comprehensive to change attitudes or behavior or to aid in practice. Recognizing that personal communication with associates is an increasingly important factor in information diffusion and technology transfer, the NIDDK continues to support vigorously the conduct of workshops, conferences, and seminars, where representatives of various disciplines can share experiences and discuss different perspectives. The Institute not only provides financial support to such meetings but sends scientific and program staff representatives to participate in discussions and present reports on the NIDDK research advances.

PROGRAM PLANNING AND ANALYSIS

The long-term goal of the Institute is development of knowledge concerning the diseases under its purview, through conduct and support of biomedical research, that would permit their prompt diagnosis, effective treatment, and, preferably, outright prevention. Shorter term objectives encompass the efficient and productive support and conduct of extramural and intramural programs of basic and clinical research related to individual diseases.

Program planning for research takes place in an atmosphere of uncertainty: conflicting sources of data must be reconciled; knowledge expands; relationships among new findings often are not evident immediately; the time frame within which new research achievements will occur cannot be predicted; and funding levels often are undetermined. Moreover, decisions regarding research must take into account issues of public health and the public's perception of health needs.

In its planning and analysis activities, the Institute complements its expertise by encouraging broad-based contributions from a variety of individuals and groups: the National Advisory Council and the two national advisory boards, ad hoc scientific advisory groups that counsel the Institute's respective Divisions and programs, other biomedical researchers, and constituent groups. Where societal choices--as opposed to administrative choices--are involved, participation of such outside advisors is especially helpful.

Planning at the NIDDK takes two major forms. The first--strategic planning--involves long-term policy development and comprehensive evaluation of opportunities and problems. This type of planning was most recently performed for the NIDDK, with the assistance of program staff, by the national commissions on diabetes and digestive diseases and by a number of evaluation panels. The other type of planning, implementation planning, is an annual process based on the findings of the more comprehensive strategic planning process; it is dynamic and of more immediate impact, focusing on what the Institute intends for the near future, usually the next 1 to 3 years.

Because the NIDDK relies heavily on investigator-initiated research, new ideas and opportunities explored by the scientific community contribute significantly to the planning process. Also, individual investigators contribute to implementation by developing research grant applications that are pertinent to announced high-priority areas.

To determine its research priorities, the Institute uses a planning process based on a series of steps involving information gathering, progress assessment, opportunity identification, and expert review. These steps, which update scientific objectives for use in making decisions on research awards, are as follows:

- Throughout the year, the NIDDK staff regularly monitors the scientific literature, conference proceedings, and progress reports of ongoing research and reviewing investigators' work. Workshops and ad hoc or formal scientific advisory groups are convened in areas of special interest. Congressional directives, plans devised by groups such as the national advisory boards, the advice of professional societies, voluntary health agencies, and consumers and the results of broad-based evaluation studies organized by the Institute (see below in section on evaluation) are all carefully studied and monitored. These data are then used for assessing progress and identifying scientific advances, opportunities, and Institute initiatives.

- The program staffs of the Institute's Divisions review such data, and each Division develops, with the assistance of its advisors, an annual research plan. The plans summarize progress, tentatively revise scientific objectives, and delineate specific new activities that show unusual promise. New opportunities and initiatives are ranked by priority on the basis of their scientific feasibility, expected costs, and expected benefits in terms of the advance of scientific knowledge and, ultimately, improved health care.

- The annual plans submitted by the Divisions are then reviewed by experts, including the Office of the Director of the NIDDK, advisory groups, National Advisory Council subcommittees, ad hoc task forces, and individual scientific experts. For example, elements of the Institute's plan are discussed formally with the Director of the NIH at an annual research-plan review session, at which senior staff members of the Office of the Director, NIH, and of the NIDDK participate. Comments resulting from further expert review are used to refine the plans.

- Once the overall plan has been approved by the Institute Director, it is presented to the Director of the NIH and to the National Advisory Council.

- The National Advisory Council and its subcommittees participate in Institute planning by reviewing the annual plans of research Divisions, making further refinements. In addition, the subcommittees and the National Advisory Council as a whole review the recommendations of peer-review groups (the NIH study sections) with regard to the funding of individual research applications.

- Taking the National Advisory Council recommendations into consideration, the NIDDK staff makes awards, giving recognition to the priority scores assigned by the peer-review groups, the Institute's financial obligations for ongoing awards made in previous years, and the amount of funds available for new undertakings.

These formal steps in the planning process are designed to ensure that the NIDDK supports new research projects of the highest scientific and technical merit, with full consideration of recent scientific progress, health care needs, and the availability of funds.

III. NIDDK SCIENTIFIC PROGRAMS

III. NIDDK SCIENTIFIC PROGRAMS

RESEARCH FOCUS--DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES

OVERVIEW

The three major program areas of the Division of Diabetes, Endocrinology, and Metabolic Diseases support the study of diseases that have devastating results in human terms. An example is diabetes mellitus, the fifth leading cause of death due to disease in the United States. Diabetes is characterized by a deficiency in insulin production or an impairment of insulin action. If the specialized cells of the pancreas that secrete insulin are damaged, the loss of the hormone can lead to various other endocrine and metabolic disturbances that affect the regulation of the body's metabolism and may lead to widespread chronic degenerative lesions that affect every tissue of the body. If the mechanisms regulating the secretion or the action of insulin are defective, similar consequences can ensue.

Endocrine and metabolic diseases may be described as specific disorders that result in generalized malfunction of the body's systems for processing information. The information being processed may be derived from genetic coding, neural transmission, hormonal messengers, immunologic responses, or cell-to-cell communication. For example, if genetic information is miscoded, the result can be an inborn error of metabolism, such as cystic fibrosis. If the hormonal and hormone-like messengers of the body are malfunctioning, the result can be an endocrine disease affecting the whole body, such as dwarfism.

Alterations in the mechanisms by which genetic and immunologic information is expressed in metabolism underlie much of the disease pathology with which the Division is concerned. The key to the successful treatment or cure of these diseases is the ability to correct the misinformation that is expressed or results in signs and symptoms of disease. At the present time, treatment measures often must focus on the repeated replacement of an absent or abnormal hormone (a failed messenger) such as insulin, but NIDDK-supported research into basic mechanisms of these diseases could lead to measures that prevent or redirect the initial failure, permitting normal functioning of the body's systems to continue.

Diabetes

Diabetes mellitus is a complex disorder of carbohydrate, protein, and fat metabolism that affects an estimated 10 to 11 million Americans, almost half of whom are as yet undiagnosed.* The diabetic condition can result in long-term complications that may involve virtually every tissue of the body, particularly the blood vessels, nervous system, kidneys, and eyes. Approximately 300,000 people with diabetes die every year; about half of these deaths are directly attributable to diabetes and its complications.* Its

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*Source: National Commission on Diabetes. On the basis of past experience, about 6.8 percent of U.S. death certificates will list diabetes as a primary or secondary cause of death. In 1985, the total number of U.S. deaths due to all causes will approach 2.1 million.

vascular complications contribute heavily to cardiovascular and cerebrovascular mortality and diabetes is a contributive factor to many more deaths. Diabetes is associated with a host of serious and widespread life-threatening complications which affect virtually every tissue in the body. The consequent loss of productivity and economic cost due to retinopathy and blindness, kidney disease, cardiovascular problems, increased susceptibility to infection, and neuropathy are considerable. In addition, diabetics spend an estimated $8 billion for medical care each year. Since 1976, the economic costs of diabetes have doubled, in terms of medical care and losses due to disability and premature death. The financial impact of diabetes now exceeds $10 billion annually.*

In general terms, diabetes can be divided into two clinical types, with different prognoses, different treatments, and different causative mechanisms. The two types are called insulin-dependent (formerly "juvenile"), or Type 1, diabetes (IDDM) and noninsulin-dependent (formerly "maturity-onset"), Type 2, diabetes (NIDDM). IDDM usually begins in early life--before age 40--and it is characterized by a requirement for daily insulin injections. Unless insulin is provided for this condition, patients will develop ketoacidosis, a buildup of acids and ketone bodies in their tissues and fluids, with a fatal outcome. Insulin-dependent diabetic patients frequently experience greatly accelerated degeneration of blood vessels in many organs, which can lead to kidney failure, gangrene in the extremities, heart attacks, stroke, neuropathy, and blindness. Even with insulin treatments, the life expectancy of such patients is measurably shortened.

About 85 percent to 90 percent of all individuals with diabetes have the noninsulin-dependent form of the disease, which usually begins after age 40 and is characterized by a slower progression of glucose intolerance and complications of the disease. Many people who have Type 2 diabetes can maintain relatively normal blood sugar levels by adhering to prescribed diets, controlling body weight, and if necessary, using oral agents to lower blood sugar levels. However, people with NIDDM may also have a decreased life expectancy because of a variety of chronic vascular and neurological complications.

During the past year, the Diabetes Research Program supported research grants and contracts in a variety of scientific disciplines that are contributing to the fundamental knowledge base needed to define the disease and its complications. Work continues on the development of improved medical capabilities for preventing, diagnosing, treating, and curing diabetes. These studies are focusing primarily on defining the natural history, etiology, epidemiology, and pathogenesis of diabetes and the resulting complications. Areas of particular research interest include studies involving islet cell transplantation (the beta cells of the pancreatic islets, which produce and secrete insulin); insulin delivery systems; secretion, transport, action, interaction, and inactivation of islet hormones; the physiology and pathophysiology of pancreatic islet cells; abnormalities of carbohydrate, lipid, and protein metabolism associated with diabetes and its complications; the possible relationships among various genetic, viral, immunologic, toxicologic, and nutritional parameters in the etiology and pathogenesis of diabetes; and the psychosocial aspects of diabetes.

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*Source: National Commission on Diabetes.

Endocrinology

The Endocrinology Program supports research into the endocrine system, one of the body's major messenger networks. The program's major emphasis is on basic research into hormone structure and mechanisms of hormone synthesis, regulation, and action. A smaller but significant portion of the program effort focuses on clinical research. Studies of thyroid, parathyroid, adrenal, pituitary, hypothalamic, thymic, and pineal hormones are supported, as well as studies on the growth factors, neuropeptides, and prostaglandins.

Basic life processes such as growth, metabolism, reproduction, and aging rely not only on the amount of circulating hormone available but also on factors within the target cells that influence the nature and intensity of the response. Moreover, a critical characteristic of the endocrine system is that few, if any, hormone-sensitive processes are regulated by a single hormone. Instead, several hormones appear to work in concert to effect or maintain body functions. Because these interactions are poorly understood, research is aimed at defining the nature of these interrelationships.

Thyroid and parathyroid diseases are among the most common in medicine. Together with adrenal and pituitary abnormalities and growth disorders, thyroid and parathyroid diseases have an enormous impact on individual well-being and on the costs of medical care. Endocrine factors also play an important role in diseases that are attributed primarily to other organ systems--for example, atherosclerosis, cardiovascular disorders, cancer, and psychiatric disorders. For these reasons, the NIDDK supports basic and clinical research on the normal and abnormal functioning of the endocrine glands; the structure, function, and mechanism of action of the hormones produced; the effects of the hormones on various processes in the body; and the factors that relate to or modify the effects of the endocrine system.

Metabolic Diseases

The primary objective of the Metabolic Diseases Research Program is to support investigator-initiated studies of fundamental metabolic processes and basic and clinical studies of various inborn metabolic diseases (cystic fibrosis, lysosomal storage diseases, glycogen storage diseases, and others). Major foci of basic research investigations include membrane structure, biological transport, and enzymatic mechanisms as they regulate normal and abnormal metabolic processes. Additional areas of emphasis include studies related to the diagnosis, etiology, pathogenesis, and treatment of a large number of inborn metabolic diseases.

Because the effects of hormones are manifested through metabolic events within the cell and because the endocrine system exerts the main regulatory influence on overall metabolism, the disciplines of endocrinology and metabolism have been intertwined, and with them, the field of genetically determined metabolic diseases. An important example of an inherited metabolic disorder with a devastating effect on its patients is cystic fibrosis, a disease to which NIDDK traditionally has devoted considerable research support. This is the most common lethal inborn error of metabolism among Caucasian children. Although the life expectancy of cystic fibrosis patients has dramatically

increased in the last 15 years, approximately 50 percent die before they reach the age of 20.

Although individual genetic disorders are not common, they have a profound public health impact as a whole. Genetic disorders account for approximately one-third of all infant deaths in the United States and approximately 30 percent to 40 percent of all admissions to children's hospitals. In addition, more than one-third of patients in state hospitals for the mentally retarded have genetically determined disorders, incurring costs for care in excess of $1 billion annually.

The NIDDK's mission in the area of metabolic diseases is to acquire an understanding of the etiology and pathogenesis of acquired or inborn errors of metabolism. To carry out its mission, the Institute supports a wide range of basic and clinical studies with the ultimate goals of improving the diagnosis of metabolic disorders, developing rational and effective methods of treatment and, where possible, achieving their outright prevention. Basic research is vital to the understanding of these diseases and includes the study of normal metabolic processes and the fate of metabolic fuels such as carbohydrates, lipids, and amino acids.

RESEARCH FOCUS--DIGESTIVE DISEASES AND NUTRITION

OVERVIEW

The Division of Digestive Diseases and Nutrition (DDDN) has responsibility for managing research programs related to liver and biliary diseases, pancreatic diseases, gastrointestinal diseases, including neuroendocrinology, motility, immunology, and digestion in the GI tract, nutrient metabolism, obesity, eating disorders, and energy regulation.

The different categories of award mechanisms utilized in this process have been described above. In addition, the division provides leadership in coordinating activities related to digestive diseases and nutrition throughout the National Institutes of Health and with various other Federal agencies. The reader's attention is directed to a detailed, Congressionally-mandated report on the Division's program of digestive diseases and nutrition centers which is being published separately.

DIGESTIVE DISEASES BRANCH

The Liver and Biliary Program supports basic and clinical research into the normal function and the diseases of the liver and biliary tract. Areas of basic research include studies on: factors initiating and maintaining hepatic regeneration; factors leading to liver cell injury, fibrosis, and death; basic and applied studies on liver transplantation, including techniques of preservation and storage; metabolism of bile acids and bilirubin; physiology of bile formation; factors controlling cholesterol levels in bile; and gallbladder and bile duct function. Areas of disease research include: cholesterol and pigment gallstones; inborn errors in bile acid metabolism; chronic hepatitis that evolves from autoimmune, viral, or alcoholic disease; and various liver diseases.

The Pancreas Program encourages research into the structure, function, and diseases (excluding cancer and cystic fibrosis) of the exocrine pancreas. Areas of research interest include: hormonal and neural regulation of electrolyte, fluid, and enzyme secretion; receptors for secretagogues; stimulus-secretion coupling mechanisms; gut-islet-acinar interrelations; organization and expression of pancreatic genes; protein synthesis and export; tissue injury, repair, and regeneration; physiology and pathology of trophic responses; innervation; transcapillary solute and fluid exchange; pancreatic transplantation, storage, and preservation; and acute and chronic pancreatitis (and relevant experimental models).

The Gastrointestinal Neuroendocrinology Program supports both basic and clinical studies on normal and abnormal function of the enteric nervous system and the central nervous system elements that control the enteric nervous system. Neuroendocrine studies supported include: histochemistry and neurochemistry, electrical properties of enteric ganglion cells, chemical neurotransmission, neural control of effector function, extrinsic nervous input. This program places a great deal of emphasis on gastrointestinal hormones and peptides. In addition, the program also supports studies on disease conditions associated with excessive or deficient secretions of neuropeptides.

The Gastrointestinal Digestion Program supports research on the process of food digestion in the gastrointestinal tract (GIT) including the synthesis and assembly of digestive enzymes; the transport of water, ions, sugars, amino acids, peptides, lipids, vitamins, and macromolecules; and chylomicron formation, structure, and function. Other areas of research focus on the regulation of gene expression in the developing GIT; the structure and function of the gut mucosa; the cytoskeletal structure and contractility in brush border; the growth and differentiation of gastrointestinal cells in normal and disease states; intestinal transplantation, storage, and preservation; and gastrointestinal tissue injury, repair, and regeneration. Also supported are studies on gastrointestinal diseases such as maldigestion and malabsorption syndromes.

Investigators supported by The Gastrointestinal Motility Program focus their research on the structure of gastrointestinal muscles, the biochemistry of contractile processes and mechanochemical energy conversion relations between metabolism and contractility in smooth muscle, extrinsic control of digestive tract motility, and the fluid mechanics of gastrointestinal flow. Other studies and areas of interest include the actions of drugs on gastrointestinal motility, intestinal obstruction, and diseases such as irritable bowel syndrome (functional digestive disorders), colonic diverticular disease, swallowing disorders, and gastroesophageal reflux.

The research emphasis of The Gastrointestinal Immunology Program focuses on intestinal immunity and inflammation. Areas of interest include: ontogeny and differentiation of gut-associated lymphoid tissue; migratory pathways of intestinal lymphoid cells; humoral antibody responses; cell-mediated cytotoxic reactions and the role of cytotoxic effector cells in chronic intestinal inflammation; genetic control of the immune response at mucosal surfaces; immune response to enteric antigens in both intestinal and extraintestinal sites; granulomatous inflammation; lymphokines and cellular immune regulation;

leukotrienes/prostaglandin effects on intestinal immune responses; T-cell mediated intestinal tissue injury; the intestinal mast cell and its role in intestinal inflammation; approaches to optimal mucosal immunoprophylaxis, including viral, bacterial, and parasitic diseases, and diseases such as gluten sensitive enteropathy, inflammatory bowel disease, and gastritis.

NUTRITIONAL SCIENCES BRANCH

This program supports basic and clinical studies related to the requirement, bioavailability, and metabolism of nutrients and other dietary components at the organ, cellular, and subcellular levels in normal and diseased states. Specific areas of research interest include the understanding of the physiological function and mechanism of action/interaction of nutrients within the body; the effects of environment, heredity, stress, drug use, toxicants, and physical activity on problems of nutrient imbalance and nutrient requirements in health and disease; specific metabolic considerations relating to alternative forms of nutrient delivery and use, such as total parenteral nutrition, and improved methods of assessing nutritional status in health and disease.

The Obesity, Eating Disorders, and Energy Regulation Program emphasizes research on the biomedical and behavioral aspects of obesity, anorexia nervosa, bulimia, and other eating disorders. The goals of such research are to establish a clear understanding of the etiology, prevention, and treatment of these multifaceted conditions. Areas of research interest focus on the physiological, metabolic, psychological, and genetic factors that affect food choices, food intake, eating behavior, appetite, and satiety; the effects of taste, smell, and gastric and humoral (including neurotransmitter) responses in association with dietary intake and subsequent behavior; the physiological and metabolic consequences of weight loss or weight gain; the effect of mild exercise on appetite and weight control, and the individual variability in energy utilization and thermogenesis.

SPECIAL PROGRAMS BRANCH

This Branch offers research training and career development awards in support of the programs of the Division of Digestive Diseases and Nutrition. Three types of National Research Service Awards and three types of research career development awards are available.

Clinical Nutrition Research Units

The Clinical Nutrition Research Unit (CNRU) is an integrated array of research, educational, and service activities focused on human nutrition in health and disease. It serves as the focal point for an interdisciplinary approach to clinical nutrition research and for stimulation of research. The Division is currently funding five CNRUs. The core center grant provides funds for (1) core resources such as cell culture, immunoassay, biostatistics, or other central research service facilities; (2) pilot/feasibility projects, which support new investigators or investigators from other fields who wish to pursue new and innovative ideas to a point where they can compete for independent support; (3) program enrichment funds to provide for small conferences or symposia, and special consultants for the center; (4) a new investigator position.

Through the CNRU mechanism, the NIH has made great strides toward upgrading the role of clinical nutrition in the participating institutions. A report on the evaluation of the CNRUs was prepared last year in collaboration with the National Cancer Institute. On the average, 23 new clinical research protocols (ranging from 7 to 40) are now active at each CNRU. Studies include the role of nutrition in growth, aging, metabolism, diabetes, cystic fibrosis, digestive diseases, renal disease, cardiovascular disease, and cancer and care of seriously ill patients. Improvements also have resulted in the coordination and delivery of nutrition-related patient care and in communication of nutrition research advances to professionals and to the public. Education of medical staffs in clinical nutrition also has been strengthened as a result of the CNRUs.

U.S.-Japan Malnutrition Panel

In 1965, President Lyndon B. Johnson and Japanese Prime Minister Eisaku Sato issued a joint communique recognizing their mutual concern for the health and well-being of all the peoples of Asia. This effort led to the foundation of the U.S.-Japan Cooperative Medical Science Program, which operates within a bilateral government framework. The Malnutrition Panel was established in 1966 to foster and support investigator-initiated research to help alleviate the serious problem of malnutrition.

National Digestive Diseases Information Clearinghouse

The National Digestive Diseases Information Clearinghouse (NDDIC) functions as the central point for the collection and dissemination of information and education materials concerning programs and resources relevant to digestive diseases. The Clearinghouse works closely with local and national digestive disease organizations, professional groups, and Federal and state agencies. The overall goals of the NDDIC are to increase knowledge and understanding about digestive diseases among patients, health professionals, and the public and to function as a catalyst in assisting and enhancing the efforts of these various groups in the development and exchange of educational materials and digestive diseases information.

Epidemiology and Digestive Diseases

The Epidemiology and Digestive Diseases Data Base System serves as the major Federal focus for the collection, analysis, and dissemination of data on digestive diseases and their complications. Drawing upon the expertise of the research, medical, and lay communities, the Data Base System initiates efforts to: (1) define the data needed to address the scientific and public health issues in digestive diseases; (2) foster and coordinate the collection of these data from multiple sources; (3) promote the timely availability of reliable data to pertinent scientific, medical, and public organizations; (4) modify data reporting systems to identify and categorize more appropriately the medical and socioeconomic impact of digestive diseases; and (5) promote the standardization of data collection and terminology in clinical epidemiological research.

RESEARCH FOCUS--KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES

OVERVIEW

The Division of Kidney, Urologic, and Hematologic Diseases administers and supports research in a broad range of basic and clinical sciences. Continual assessment of the programs of the Division is based on liaison with extramural scientists, including ad hoc advisory committees. This evaluation process allows the Division to facilitate support mechanisms for important new areas of research which are most responsive to the needs of the research community and ultimately to the needs of patients with urinary tract and hematologic diseases.

The diseases and disorders for which this Division is responsible include some of the Nation's most critical public health problems. Kidney and urinary tract diseases alone affect over 13 million Americans and account for more than 80,000 deaths each year. In providing maintenance dialysis and kidney transplantations for more than 80,000 patients with end-stage renal disease, the Federal Government spends over $2 billion each year.* In 1978, blood diseases were reported to be an underlying cause of over 350,000 deaths.

The programs of this Division are keyed to these public health problems. The Renal Physiology/Pathophysiology Program aims to discover the underlying mechanisms of kidney disease through studies of normal structure and function of the kidney, including its metabolism, transport, and fluid-electrolyte dynamics. Of high priority in this program is research on immune diseases of the kidney, including glomerulonephritis and interstitial nephritis. These diseases are the cause of end-stage renal failure in almost half the patients seen in centers of dialysis or transplantation. The Division is taking special action to stimulate research on immunologic mechanisms pertaining to the pathogenesis and treatment of chronic renal diseases. Additional special emphasis areas include other diseases and mechanisms leading to chronic renal disease, such as diabetic nephropathy, hypertension, lupus nephritis, and polycystic kidney disease, and effects of drugs, nephrotoxins, and environmental toxins that adversely affect the kidney, including analgesic abuse and heavy metal toxicities.

The kidneys are vital organs critical to the maintenance of the body's internal environment, particularly the composition, volume, and pressure of the body fluids. In past years, such research has increased our knowledge of renal metabolism and the causes of renal disease and has resulted in the development of several lifesaving measures.

In the Chronic Renal Disease Program, studies focus on the metabolic and systemic abnormalities of uremia, a toxic condition that develops once renal failure is advanced sufficiently. The program supports research on the pathophysiology of chronic renal failure, the medical and surgical aspects of renal transplantation, and the various therapies involved in maintenance dialysis. A growing focus of this program is research to determine the impact

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*Health Care Financing Administration.

of dietary protein restriction on the progression of chronic renal disease. A collaborative clinical study of the effect of dietary modification on the course of progressive renal disease is now being organized.

Advances that have resulted from these investigations make useful lives possible for many patients who otherwise would have died after loss of kidney function. For example, hemodialysis, the use of an artificial kidney machine to remove poisonous wastes directly from the blood, has been improved through new techniques; peritoneal dialysis, a procedure for clearing toxic waste across the peritoneal membrane, has become a clinically effective alternative to hemodialysis in the treatment of end-stage renal disease (ESRD); and kidney transplantation has evolved from a method of last resort to the treatment of choice for certain patients.

The Chronic Renal Disease Program supports research in both fundamental and clinical investigation of disease mechanisms responsible for ESRD, its complications, and all aspects of its treatment.

Inseparable from the function of the kidneys is the function of the lower urinary tract, the primary concern of the Urology/Urolithiasis Program. Urinary tract infection, neuromuscular disorders of bladder function, obstruction, and urolithiasis, or kidney stone disease, account for about 20 percent of deaths from kidney disease. Together, these interrelated conditions account for a major portion of all disability caused by disorders of the urinary tract.

To provide insight into the causes and development of these multiple diseases, the program supports research ranging from fundamental studies such as the kinetics of urinary stone development, and the dissolution of stone-forming materials, to applied projects such as the comparison of medical versus surgical therapy for vesicoureteral reflux in children. Conditions such as Peyronie's disease, impotence, congenital anomalies of the lower urinary tract, and others, are included. Among the high incidence urologic diseases emphasized in these studies are urinary tract infections, reflux nephropathy, urolithiasis, and benign prostatic hyperplasia. A program of Specialized Centers of Research in Urolithiasis was pursued during 1977-1980 and was very successful in increasing the research effort and consequent research advances which made possible the prevention of recurrences of urolithiasis in large numbers of patients. Program staff members are now stimulating a concerted cross-disciplinary approach to research in benign prostatic hyperplasia. Special efforts are also under way to elicit proposals on impotence and on urinary tract infections.

As the result of NIDDK support of research in these areas, new drugs have been developed that permit effective treatment of serious infections and prevent recurrence of certain types of kidney stones, and advances in urologic surgery have led to the ability to repair congenital anomalies and surgically reconstruct diseased organs.

The Division's Hematology Program supports investigation into basic mechanisms of normal blood cell function and into pathogenesis of hematologic disorders, including development of treatment and prevention modalities,

clinical application, and evaluation of treatment. In addition, the ready availability of blood and blood cells facilitates study of membrane phenomena, protein structure and function, and similar topics broadly applicable to general medical problems. Since its inception 30 years ago, the Hematology Program has placed major emphasis on the cutting edge of basic research and has related closely to other NIDDK programs.

The NIDDK supports hematologic research as a part of its mission to eliminate the threat of the chronic diseases that cause suffering, disability, and early death. Many of these chronic diseases exhibit manifestations that include anemia, caused by impaired or abnormal red blood cell production or by inherited defects in red blood cell components. Anemias of chronic disease rank high among the clinical disorders that threaten life or diminish the quality of life. The anemia of chronic renal disease occurs in most of the chronic renal disease patients treated annually in the United States. Anemia is commonplace in patients with endocrine disorders, the collagen diseases, rheumatoid arthritis, ulcerative colitis and other digestive diseases, liver disorders, nutritional deficiencies, and a variety of inflammatory syndromes. These anemias, all of which are acquired secondary to chronic diseases, fall within the NIDDK responsibility because of the NIDDK mission related to hematology, renal disease, endocrine disorders, arthritis, and digestive and nutritional diseases.

Basic and clinical research of particular interest includes anemias of genetic origin, nutritional anemias, metabolic disorders, disorders of blood cell production, and autoimmune hematologic disease. Research studies in these categories, which are coordinated closely with other NIH blood disease programs, range from determination of the molecular structure of abnormal types of hemoglobin, the protein that enables red blood cells to act as oxygen carriers, to clinical application and evaluation of new treatment methods of certain hematologic disorders such as aplastic anemia, Cooley's anemia, and sickle-cell disease. This research has increased both fundamental and applied knowledge about blood and has led to improved management of many specific diseases.

Congenital or hereditary anemias generally result from some specific fixed disorder in body chemistry and metabolism or molecular design. Research support for hereditary anemias has led to a nearly complete analysis of normal and certain abnormal human hemoglobin gene sequences and to safer and more accurate techniques for prenatal diagnosis of sickle cell disease and Cooley's anemia. Basic work on the hemoglobin molecule has been instrumental in establishing concepts in molecular disease, and today hemoglobin and hemoglobin diseases represent models for research progress in other genetic diseases.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Obligations by Scientific Program
Fiscal Year 1985
(Amounts in thousands)

Disease Category	Research Grants: Research Projects	Research Grants: Research Centers	Research Grants: RCA & Other Research	Training	Research & Development Contracts	Subtotal Grants & Contracts	Intramural Laboratory & Clinical Research	Total Program	With Admin. Costs
Diabetes	66,526	13,964	1,882	4,974	4,534	91,880	8,625	100,505	103,977
Endocrinology	35,235	—	1,346	2,758	1,411	40,750	12,916	53,666	55,363
Metabolism	44,417	808	1,567	1,428	206	48,426	19,430	67,856	70,001
Subtotal	146,178	14,772	4,795	9,160	6,151	181,056	40,971	222,027	229,341
Sci. Eval/MBS	4,504	—	4,336	571	—	9,411	—	9,411	9,709
D, E, & M	150,682	14,772	9,131	9,731	6,151	190,467	40,971	231,438	239,050
Digestive Diseases	53,563	7,184	2,326	4,420	725	68,218	4,620	72,838	75,415
Nutrition	12,798	2,991	77	1,173	91	17,130	2,459	19,589	20,210
DD & N	66,361	10,175	2,403	5,593	816	85,348	7,079	92,427	95,625
Kidney, Urology	55,193	—	2,398	3,487	212	61,290	2,243	63,533	65,543
Hematology	23,809	—	1,295	1,764	693	27,561	2,102	29,663	30,601
K, U, & H	79,002	—	3,693	5,251	905	88,851	4,345	93,196	96,144
Total	296,045	24,947	15,227	20,575	7,872	364,666	52,395	417,061	430,819
						Research Management and Support		13,758	
						Total		430,819	

APPENDIX 1
RECENT NIDDK RESEARCH ADVANCES
Specific Examples From Each Scientific Program

RECENT RESEARCH ADVANCES

Specific Examples from Each Scientific Program

DIABETES

Insulin Biosynthesis and Secretion

Prior Findings

Insulin is synthesized and then secreted (released) from the beta cells in the islets of Langerhans of the pancreas in a complex series of steps. First, a very large protein molecule, pre-proinsulin, is synthesized. Then a part of the molecule is split off to leave the proinsulin residue. This in turn is divided by two cleavage steps to remove another peptide chain of amino acids (the C-reactive peptide) from the middle of the proinsulin molecule. The resulting two peptide chains of amino acids are chemically linked together by disulfide bonds. Normally it is this form of insulin which is secreted together with the C-reactive peptide. Since the C-reactive peptide is made by cleavage of the proinsulin molecule, normally it is secreted in equal quantities with insulin.

Disturbance of this process of synthesis and secretion at any point in its sequence can lead to derangements in insulin secretion. A great deal of attention has been given to disorders associated with the stimulating effects of glucose and other hormones on insulin secretion. Less common are derangements of insulin secretion which result from the synthesis of abnormal pro-insulin materials.

Recent Advances

A recent study described a new familial defect in insulin secretion which results in faulty conversion of proinsulin to insulin. In contrast to two earlier instances, in which the conversion defect was due to abnormal structure of the proinsulin molecule, this family had beta cells in which the proteolytic enzyme(s) which convert proinsulin to insulin appear to be defective.

High circulating levels of immunologically reactive insulin (total proinsulin plus insulin) were found in affected family members over a span of three generations. This was found to be due to a marked increase in the proportion of proinsulin-like material in their blood because of impaired conversion of proinsulin to insulin. In affected family members the ratio of C-reactive peptide to immunoreactive insulin was decreased but the ratio of C-reactive peptide to total circulating insulin itself was normal, as would be expected.

Research Directions

A detailed understanding of where and how the beta cell processes its secretions is essential if we are ultimately to influence and control insulin secretion to maintain euglycemia. Such information is potentially useful in identifying secretory dysfunctions in the diabetic state.

ENDOCRINOLOGY

Obesity May Lead to a Defect in Pituitary Gland Responses

Prior Findings

Obesity is known to be associated with blunted responses to stimuli that cause release of growth hormone (GH) by the pituitary gland, reversible after successful weight reduction. The availability of growth hormone releasing factor (GRF) has now permitted researchers to distinguish between the hypothalamic region of the brain and the pituitary gland itself as a locus of the defect, and to decide whether the defect is a cause or a result of obesity.

Recent Advances

Patients with morbid obesity were evaluated, before and after therapeutic gastrointestinal surgery for obesity, for their ability to secrete GH in response to GRF, on the one hand, and to insulin-induced hypoglycemia (fall in blood sugar), on the other. The pattern of results suggested that the diminished response to insulin hypoglycemia was mediated by an impaired pituitary gland response to GRF, and not a defect in the hypothalamus. Reversibility after weight reduction suggests that this is a result and not a cause of obesity.

Research Directions

Specific mechanisms for the pituitary gland defect in morbid obesity need to be established, including the role of substances that can inhibit GH release (such as the hormone somatostatin).

METABOLIC DISEASES

A Molecular Basis for Disease Susceptibility

Prior Findings

It is often speculated that susceptibility to a specific disease may be partially genetic or inborn, but the mechanism for this susceptibility is most often elusive. In a type of severe and ultimately fatal glomerulonephritis known as Goodpasture's syndrome, which also involves serious lung pathology with pulmonary hemorrhages and respiratory failure, a molecular basis for the autoimmune defect, or the formation of antibodies against one's own tissues, has been sought.

The glomeruli are capsule-like components of the kidney in which blood vessels terminate and the separation of the urine is initiated. Goodpasture's syndrome results in kidney failure, due to the individual's production of an antibody to an antigen found in the glomeruli of the kidney. The antigen-antibody complex accumulates in one of the glomerular membranes, called basement membrane, and causes inflammation of the capillary loops (glomerulonephritis). A simultaneous and similar process takes place in the alveoli (tiny bellow-like structures) of the lung when antigen-antibody complexes are deposited in the

alveolar-capillary basement membranes. Approximately 5 percent of all cases of glomerulonephritis are of Goodpasture's type. The disease is a model of autoimmune disease caused by immune complexes; there was evidence suggesting a strong immunogenetic susceptibility to this disease, reflecting the activity of an immune response gene. Therefore, identification of Goodpasture's antigen is of importance in understanding the exact nature of the disease and designing specific therapies.

Recent Advances

Researchers supported by the Institute have recently established that the antigen in Goodpasture's syndrome is a degradation resistant noncollagenous fragment of collagen (type IV), a tissue-supportive protein of the type found in the basement membrane. The fragment is resistant to collagenase, the enzyme which breaks down collagen, and it was therefore isolated from bovine and human glomerular basement membranes which were digested with collagenase.

The identity of this collagen derived fragment and Goodpasture's antigen was demonstrated by developing antibodies to it and by comparing the reactions of serum from Goodpasture's patients and from pooled normals to the Goodpasture's antigen. While sera pooled from a large population of normals showed insignificant binding, all Goodpasture's patients' sera reacted with the antigen preparations.

Research Directions

These studies indicate that Goodpasture's antigen is contained within the collagen of the glomerular basement membrane, localized to the noncollagenous sequences of the molecule. They facilitate the understanding of the pathophysiology of this autoimmune disease and open new avenues for understanding immunogenetic susceptibility. These findings also contribute to understanding the structure of the basement membrane, and may help define its role or functioning in other diseases. Research is needed to clarify and extend progress in each of these problem areas. Immediate work should attempt to define the exact structure of the antigen, to design a specific assay for early diagnosis of Goodpasture's syndrome, and even to eliminate antigen antibody complexes from patients with the disease.

DIGESTIVE DISEASES

Hepatic Porphyrias: Advances in Understanding and Treatment

Prior Findings

The porphyrins are pigments widely distributed throughout nature; the several types have in common the porphyrin ring structure, made up of four subunits known as pyrroles, each derived from two molecules of aminolevulinic acid (ALA). The most abundant porphyrin in man is heme, found in hemoglobin (which is degraded in the body to form other porphyrins, the bile pigments), and in myoglobin (the oxygen carrier protein in muscle), as well as in respiratory enzymes such as the cytochromes.

Heme (iron protoporphyrin IX) is involved in vital cellular functions of all aerobic animals, and its metabolism is extremely well regulated. However, certain genetically determined enzymatic lesions occur in humans which lead to heme-deficient states, known as the porphyrias. In porphyric individuals exposure to a variety of factors, including drugs and diet, frequently precipitates acute life-threatening attacks characterized by grave central and peripheral nerve damage. In these individuals intravenous heme dramatically relieves the symptoms and corrects the biochemical abnormality.

The clinical features of an acute attack are all due to dysfunction or death of neurons; the usual attack is limited to acute pain with autonomic dysfunction, i.e., abdominal pain that is severe and remitting for hours to days. Less frequently, the more severe attack has peripheral motor dysfunction with muscle weakness. These attacks may progress to global central nervous system dysfunction including delirium, seizures, coma, and death.

Misdiagnosis at times leads to administration of barbiturates as anesthetics or sedatives, usually with disastrous results since barbiturates and other drugs like estrogens, halothane, and meprobamate may precipitate an acute attack of porphyria. This makes treatment of the seizures very difficult because the usual drugs of choice for seizures are contraindicated in porphyria. Recently hematin (solubilized heme) has been used intravenously to terminate acute porphyric attacks. Hematin is being developed as an "orphan drug" for this condition. It is known that heme exerts a feedback inhibition on the rate-limiting enzyme in heme production (ALA synthetase) and thereby cuts back on the overproduction of ALA and subsequent porphyrins. What is not known is how this effect on liver enzymes can influence the neurologic attack since injected heme is unlikely to penetrate into the central nervous system.

Recent Advances

An NIDDK-supported research team has reported that acute hepatic heme deficiencies result in increased brain levels of tryptophan and serotonin, in an animal model, which may be the cause of the neurological disorders seen in human porphyria patients. The team examined the brains of rats with an induced acute hepatic heme deficiency. This was accomplished by giving phenobarbital to create an increased demand for heme (as cytochrome P_{450}), followed by an injection of a compound which destroys the P_{450} and the heme. This model resulted in a 50 percent decrease in hepatic heme within 4 hours and a six to eightfold increase in excretion of urinary porphyrin compounds.

The decrease in liver heme was associated with a dramatic reduction of hepatic tryptophan pyrrolase, an enzyme (a heme protein) known to be regulated by the free heme pool. This enzyme is responsible for degrading tryptophan and in its absence, tryptophan concentration rises in the plasma and in the brain. Tryptophan is converted to serotonin in the nervous system. In other conditions in which circulating tryptophan is increased experimentally, structural alteration of brain neurons and wasting of axons has been produced. Similar alterations have been reported in cases of acute porphyric attacks, but whether elevated serotonin can be implicated in such pathogenic changes remains to be determined. Pharmacologic effects of serotonin in the brain

and in the GI tract resemble the neurological manifestations of acute porphyric attacks. The decreased tryptophan pyrrolase activity persisted over 32 hours, during which time brain tryptophan and serotonin and a serotonin metabolite (5HIAA) remained high. These effects could be reversed quickly (within 5 hours) by the parenteral administration of heme (11 mg/kg).

This is the first demonstration of an alteration of a vital neurochemical within the central nervous system being elicited by acute hepatic heme deficiency and reversed by exogenous heme administration.

Research Directions

Because of the relative impenetrability of the blood-brain barrier to exogenous heme, the mechanism of action of heme in the acute hepatic porphyrias has proved elusive. The role of tryptophan pyrrolase in the human diseases must now be ascertained, with further studies of the liver enzymes, and of blood levels and cerebrospinal fluid levels of the key enzyme in humans.

NUTRITION

Sensitive Assessment of General Nutritional Status by Somatomedin-C Level

Prior Findings

Of the tens of millions of people hospitalized each year, over 40 percent have been found to be malnourished. Without a means of early recognition of this problem, the malnutrition can worsen during the hospitalization and can interfere with medical or surgical treatment measures. Early recognition and intervention to correct nutritional problems have been shown to lessen morbidity and mortality, as well as to improve immunologic function and postoperative wound healing.

Of the available methods for diagnosis of protein and calorie malnutrition, and for following the response to nutritional therapy, none is sufficiently sensitive to short-term changes in nutrition or sufficiently specific for malnutrition as opposed to effects of various disease processes, to supplement or improve on bedside clinical judgment. Among these methods are measurements of skinfold thickness, muscle-circumference, percent of ideal body weight, blood protein levels (albumin and transferrin, the iron-transport protein, as well as proteins that bind thyroid hormone and vitamin A), and blood lymphocyte levels (lymphocytes are the key cells in immunity).

Because it had been noted that the serum growth factors known as somatomedins decrease with undernutrition and rise with refeeding, in a manner correlated with the type of nutrient over the course of a single day, researchers decided to evaluate their usefulness in nutritional assessment in the presence of other diseases. These insulin-like substances are made in the liver, depend on growth hormone and show tissue-building (anabolic) activity, and appear to be part of the hormonal adaptation to nutrient levels. In humans, somatomedin-C is the one most of interest here.

Recent Advances

Of 28 patients malnourished by available criteria, who entered the study before nutritional therapy was used, 13 had cancer (pancreas, colon) and 9 had gastrointestinal diagnoses (Crohn's disease, peptic ulcer); the rest had neurologic and other diagnoses. Their somatomedin-C levels were reduced (to an average of 38 percent of normal), ranging from 25 percent of normal in the most severe deficiency to 57 percent of normal in the least severe. In six of these patients who agreed to testing during nutritional therapy, somatomedin-C levels rose by more than 70 percent in each. In 20 patients with detailed dietary analysis, only somatomedin-C was correlated with recent intake of protein and calories. Other methods of assessment already mentioned (albumin and transferrin levels, lymphocyte count, skinfold thickness, muscle circumference) were not as depressed before therapy and did not rise as much during therapy. It was concluded that somatomedin-C shows superior sensitivity to altered nutrition and is more specific as well. Levels of this growth factor are normal if patients are receiving more than 1.6 grams of protein per kg body weight.

Research Directions

Further studies are required to confirm and evaluate the sensitivity and specificity of somatomedin-C measurements in assessment of nutritional status, and the use of such measurements in predicting nitrogen balance during nutritional therapy. Study of the mechanism of or basis for these correlations should suggest other types of nutritional assessment measures, and should provide useful insights for both endocrinology and nutrition.

The Effects of Weight Loss in Obese Diabetic Patients

Prior Findings

Both obesity and diabetes are associated with resistance to the action of insulin in controlling blood sugar levels. Noninsulin-dependent diabetic patients (NIDDM, or Type 2 diabetes) are frequently obese, and weight reduction is generally recommended. In the absence of weight reduction, both conditions are associated with increased risk of cardiovascular disease and other complications, and obesity is associated with increased risk of the emergency of Type 2 diabetes in individuals with the inherited trait for the disease.

The obese diabetic individual finds it difficult to lose weight with conventional caloric restriction diets. Such measures as liquid protein diets and gastric bypass surgery are more effective, but not enough is known about their safety or their effects on control of blood sugar levels. Obese diabetics also have a defect in insulin release, which further complicates effects of treatment.

Recent Advances

To examine the effects of weight loss in obese diabetics, and the relationship of obesity to concurrent diabetes, NIDDK-supported researchers studied

weight reduction by dietary means (caloric restriction with a protein supplement at 1.4 g/kg ideal body weight) and gastric bypass surgery, each in a group of six obese diabetics. Each patient was more than 30 percent overweight by standard tables; those more than 90 pounds overweight were placed in the surgical therapy group. Both treatment methods improved control of blood sugar (the average fasting glucose level fell from 287 to 168 mg/dl, and the glycosylated hemoglobin, from 11.9 to 8.2 percent, both significant declines)--the greater the weight loss, the better was the control achieved. In the diet group, effective control resulted from caloric restriction, even prior to significant weight loss.

Improved control of blood sugar was accompanied by decreased resistance to insulin (and a fall in fasting insulin levels), although insulin release (acute-phase, or initial release, which was impaired prior to treatment) did not improve. This suggests that impairment of the pancreatic beta cells persisted. The degree of improvement in insulin resistance was correlated with the amount of weight loss, a finding consistent with other work.

Importantly, both methods of treatment reduced the risk factors that lead to atherosclerosis. The protective (high density) lipoprotein values increased significantly. Blood coagulation factors (factor VIII and fibrinogen), which are increased in diabetes and accelerate atherosclerosis, were lowered.

Both weight reduction methods were judged safe and effective, and were not associated with side effects (such as changes in heart rhythm from the liquid protein diet) sometimes reported. The resulting weight loss was highly beneficial to the patients, by control of blood sugar levels and by lessening risk of cardiovascular disease.

Research Directions

The mechanism of the decrease in risk factors for vascular damage from fat deposits--the role of lowered blood sugar as compared with that of weight reduction and of coagulation factors--requires further study. The nature of the defect in insulin release in diabetes, which persists after treatment (along with abnormalities in clearance of high sugar levels from the blood) is a focus of continuing investigation. Long-term safety and efficacy of such methods is a major issue yet to be resolved.

KIDNEY DISEASES

Chronic Renal Failure: Prevention and Treatment by Diet

Prior Findings

Chronic renal failure characteristically progresses inexorably toward end-stage renal insufficiency. The rate of loss of residual renal function varies widely among patients, but in most subjects the rate of progression, once established, remains remarkably constant, suggesting that renal damage occurs constantly even in patients whose initial disease is no longer active.

The basic principle for the management of end-stage renal insufficiency is the restriction of protein intake. It is clear that accumulation of nitrogenous metabolites plays a major role in the pathogenesis of the uremic syndrome. This observation is based on findings that in patients with chronic renal failure, the institution of a protein-poor (low nitrogen) diet results in improvement of the general condition, disappearance of uremic symptoms and decreased serum urea concentration.

Several recent studies suggest that nutritional and metabolic factors may have a considerable effect on the rate of progression of renal diseases. The evidence, although not conclusive, indicates that low protein diets, particularly when associated with careful control of phosphorus intake, may retard the rate of progression of renal failure in animals and humans.

Since a source of essential amino acids is required to meet the daily demands for protein synthesis within the body, the effect of dietary prescriptions of essential amino acids and of their nitrogen-free (keto) analogues is being experimentally utilized in the management of chronic renal failure, as well as other diseases. These compounds lack (the alpha-amino) nitrogen but are rapidly converted to amino acids in vivo; therefore, administering them may be almost tantamount to providing the needed essential amino acids without necessarily increasing the nitrogen burden which the failing kidney has to cope with.

Recent Advances

A clinical trial under NIDDK support indicates that a low-phosphate/protein restricted dietary prescription, supplemented with a mixture of essential amino acids and ketoacid analogues of essential amino acids, can slow or arrest the progression of renal insufficiency, especially if initiated early in the chronic renal failure process.

Twenty-four patients with progressive renal insufficiency received a dietary prescription consisting of a low phosphorus intake (less than 600 mg/day) and 20 to 30g per day of mixed quality protein, supplemented with essential amino acid-ketoacid mixtures, at a dose of 18g/day (1.8g of nitrogen); supplemental calcium was added to provide a total calcium intake of 1.5g/day, along with the B vitamins and vitamin C, and sodium bicarbonate to control metabolic acidosis. Ten of the 17 patients with well-defined rates of progression of deterioration of renal function had a significantly slower rise in creatinine levels (a measure of the degree of renal failure) during an average of 20 months of long-term treatment than perdicted; none had a faster rise than predicted. Seven of the 17 patients began the dietary treatment before the serum creatinine reached the level of 8 mg/dl; in 6 of the 7 followed for an average of 22 months, creatinine remained at or below the level at the start of treatment. Nutrition, as assessed by body weight, nitrogen balance, serum albumin, and serum transferrin (a protein that transports iron and which, when depressed, reflects malnutriton) was well maintained.

This regimen caused a substantial decrement in the rate of progression of renal insufficiency, especially when the dietary treatment was initiated before creatinine levels reached 8 mg/dl.

Like all other studies of the progression of chronic renal failure reported to date, this one lacked a randomized control study group. The conclusions drawn depend on the validity of using each patient as his/her own control to evaluate changes in the rate of progression of the renal process. Nonetheless, these results indicate that a low-protein, low-phosphorus diet supplemented with essential amino acids and their keto acid analogues has the potential of substantially influencing the course of progressive chronic renal failure.

Research Directions

Work is needed to further the understanding of the basic mechanisms by which progression of established chronic renal disease progresses to end-stage renal failure, and to define the role of dietary interventions in the management of progressive renal insufficiency.

UROLOGIC DISEASES

Benign Prostatic Hyperplasia: Understanding Abnormal Growth

Prior Findings

Benign prostatic hyperplasia (BPH) is characterized by excessive growth and expansion of the prostate gland, usually in elderly men and frequently associated with retention of urine and disruption of normal voiding.

The primary goal of research in this area is to continue to stress multidisciplinary approaches to assessing normal and abnormal growth of the prostate gland, to understand better the onset and progression of BPH. The morbidity and estimated medical costs associated with BPH, which exceed $1.5 billion annually, make this disease a significant national health problem. It occurs in younger as well as older males. The disease has been detected as early as age 20. Typically, it begins in the third to fourth decade of life. It occurs frequently, with evidence of symptomatic disease in about 45 percent of men at age 45 and nearly 80 percent in men over 60. Up to 10 percent of all prostatic specimens obtained from surgery for BPH show microscopic evidence of cancer (adenocarcinoma).

Methods have been developed for separating stromal (nonglandular framework) tissue, and surface (epithelial) tissue of the prostate. Studies suggest that human BPH results from induction of embryonic growth potential present in stromal components.

The nuclei of tissue taken from patients with BPH have higher concentrations of dihydrotestosterone receptors than nuclei taken from normal prostates, whereas total prostate gland contents of androgen are the same for BPH and normal glands. A major proportion of the steroid-binding capacity of cell nuclei from prostate tissue is contained in the nuclear matrix, which also serves to anchor certain DNA sequences and RNA processing.

Recent Advances

Factors responsible for the renewed growth of the prostate continue to be investigated. It seems clear from information presented at the recent NIDDK-sponsored symposium on BPH (please see "Program Accomplishments") that endocrine parameters are no longer thought to be causative, but may act in a permissive way allowing a renewal of embryonic growth potential in the gland. It is clear that the amount of growth shown in BPH far exceeds that which can be induced simply by hormone regimens.

Several specific advances may be mentioned:

The testes apparently secrete a nonandrogen substance, as yet unidentified, associated with BPH in animal models.

Autoradiographic analysis of human BPH tissue reveals that the androgen receptor is predominantly located in epithelial nuclei, with little or no receptor function in the stroma.

An activated androgen-receptor complex has been shown to bind with high affinity to acceptor sites on the internal RNA-protein network of the nuclear matrix.

Vitamin A (retinol) causes approximately 40 percent inhibition of estrogen (3H-estradiol) binding to estrogen receptors in the cytoplasm. A potential role for vitamin A in down-regulation of estrogen binding has been suggested recently, and this in turn might relate to BPH.

The prostate itself may contribute a protein capable of stimulating growth (prostatic growth factor). Both tissue and prostatic secretions may contain this growth factor, capable of inducing true mitogenic (cell division) activity in the prostate gland. Research has yet to purify this substance; however, it is known that the prostatic growth factor does not cross-react with any of the other known and relevant growth factors. Current advances have yet to provide information on its relationship to the abnormal prostatic growth with its associated urine retention or disrupted micturition.

Whether renewed growth results from a prostatic growth factor or other collagen derived factor remains an open question; another possibility recently increasingly considered is whether a "braking" system ceases to operate against further prostatic growth in middle years. One postulate is that there is a renewal of an embryonic induction of growth in the prostatic stroma, as already noted.

Research Directions

Research should continue present efforts to identify and purify a prostatic growth factor, or other factors, which may be responsible for growth of the prostate, and further delineate the role of androgens in allowing either renewed growth or removal of a "brake" to further growth during specific time periods. This may be facilitated by obtaining workable quantities of purified androgen receptor protein, then antibody might be generated against the

androgen receptor, thus facilitating our efforts to isolate the gene. Such studies could further question whether subtle changes have occurred in the dynamics of the hormone-receptor complex which may predispose the prostate to renewed growth.

The apparent close association in the nuclear matrix of bound androgen hormone and certain nucleic acids may offer further understanding of hormone-gene interactions, a major area of research attention shared with many other disciplines.

HEMATOLOGIC DISEASES

Improved Nutritional Support in Sickle-Cell Disease

Prior Findings

Children with sickle-cell disease commonly are retarded in growth, and several vitamin and mineral deficiencies have been reported. In addition, defects in fat absorption or metabolism have been reported.

Recent Advances

A recent study assessed the effect of various kinds of nutritional supplementation on a sample of five boys affected with sickle-cell disease. All were severely growth retarded (in the lowest 5 percent for their age group). Calorie and protein intakes were normal, and intestinal absorption was unimpaired.

Two of the boys were placed on vitamin and mineral supplements and given nutritional counseling, but no other dietary supplements. Their height and weight remained below normal for their age groups. A third boy, given supplemental feedings by mouth, did not change in growth rate, but appeared to gain in health status, requiring fewer hospital admissions for his sickle-cell disease. The other two boys, given supplements by feeding tube, increased dramatically in both height and weight. Neither required further hospital admissions.

Research Directions

The reason for the increased metabolic requirements of patients with sickle-cell disease remains to be worked out. These results, however, suggest that both growth rate and overall health of patients with this illness may benefit dramatically from nutritional supplementation via feeding tube.

APPENDIX 2
NHLBI Research Related to Programs of NIDDK

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI) RESEARCH RELATED TO PROGRAMS OF NIDDK

The NHLBI supports research, largely through the mechanism of grants, but to some extent through contracts, and intramural research, in fields that are complementary to areas of interest to NIDDK. Noted below is research on certain complications of diabetes; on the kidney in hypertension; on kidney disorders; on lipid metabolism; and on nutrition as these affect cardiovascular, lung, and blood disorders.

Diabetes

Diabetes is a major risk factor for cardiovascular disease including heart attack, stroke, peripheral vascular disease and hypertension. Because these complications are promoted by both type I and type II disease, the NHLBI supports an appreciable program devoted to research on cardiovascular complications of diabetes and their underlying mechanisms. Support is provided to cardiovascular-diabetes fellowships and training on a small scale; there are eight F32 awards, eight in the K-series, and one T32. In addition 167 grants or contracts have a component of diabetes research. Of these, the component amounts to 50 to 100% of effort in 45, while it is 10% or less in 79.

Lipid metabolism in diabetes is the most common subject for study, amounting to 61 awards. Disorders of the heart and circulation (including peripheral vascular disease and hypertension) follow with 54 awards. Macroangiopathy is the subject of 22 awards. Epidemiology (diabetes in association with cardiovascular disease) accounts for 14 awards and disorders of blood coagulation and platelet pathophysiology for 10. There are no grants dealing with the etiology and pathogenesis of diabetes per se. One grant deals with pancreatic elastase.

Total diabetes related research supported by NHLBI in FY 1985 amounted to 184 projects at an estimated cost of $19,135,000.

Hypertension Related to Kidney Disorders

The Hypertension and Kidney Diseases Branch of the Division of Heart and Vascular Diseases supports research on the maintenance of the normal and abnormal blood pressure. Many factors may be involved in this complex pathophysiology including enzymes secreted by the kidney and neurohumoral agents acting upon it; local vascular and cardiac phenomena; blood volume and dynamic changes; central and peripheral nervous system effects and electrolyte balance may, among others, be involved.

The Branch does not support research on diseases in which the kidney is a target organ (except hypertension) such as inflammatory diseases, autoimmune disease, stone, diabetic nephropathy, amyloid, or upon end-stage renal disease, its complications, prevention or treatment. On the other hand there is active support for studies involving the kidney and blood pressure, such as research on the renin system, kallikrein-kinins, vasopressin, renal innervation,

the renal circulation in hypertension, reno-renal reflexes, antihypertensive reno-medullary hormone, renal dopamine receptors, interactions with prostanoids, effects of epinephrine, sodium and potassium handling, sympathetic nervous system in sodium dependent hypertension, renal input to spinothalamic neurones, the cellular biology of the juxtaglomerular apparatus, renin gene expression in hypertension, and so on.

The focus of the renal studies is the primary or secondary role of the kidney in the normal or abnormal homeostasis of the blood pressure in acute and chronic circumstances.

Since the contractility and responsiveness of the (arteriolar) vascular smooth muscle cell are central to the control of the peripheral vascular resistance, the physiology of this cell, its membrane pumps and channels and its contractile protein are also of interest to the Branch. In this respect sodium, potassium, calcium, and magnesium are of interest at both the cellular and nutritional levels.

Total NHLBI extramural research support by NHLBI in FY 1985 in this program area amounted to 85 projects at an estimated cost of $14,318,000.

Kidney Disorders

The NHLBI intramural research program related to kidney disorders is conducted in the laboratory of Kidney and Electrolyte Metabolism. The overall goal of the laboratory is to analyze the function of the kidney as a basis for understanding its pathophysiology and treating its disorders. Since the formation of urine depends upon the transport of water and solutes by kidney tubules, understanding renal function requires analysis of these cellular processes and of their integration in the kidney. Therefore, transport by cells in general and kidney cells in particular, as well as the mechanisms, hormonal and other, that control transport are under investigation.

In FY 1985, the laboratory supported research projects on isolating segments of renal tubules, developing mathematical models of renal function, studying the regulation of amphibian epithelial cell volume and solute transport, exploring the cell culture of epithelia, and investigating metabolism associated with solute transport.

Lipid Metabolism

Lipid metabolism, because of its associations with experimental and human atherosclerosis, has been a major subject of interest to the Lipid Metabolism and Atherogenesis Branch of the Division of Heart and Vascular Diseases. Research has been supported at the most basic molecular level, at the level of animal and clinical investigation, with the participation of cohorts in prevalence and randomized clinical metabolic trials, and at the public health level of demonstration and education programs concerning dietary fats and cholesterol.

Interest in lipid metabolism is heavily concentrated on lipoprotein and cholesterol metabolism with somewhat lesser emphasis on triglycerides and

dietary fatty acids and less on phospholipids. Subsets of interest involve long chain n-3 fatty acids and the prostaglandin family.

Some investigators study lipoproteins and apoproteins together, some study them separately and specifically, and others are interested in their heterogeneity and metabolic coordination. VLDL, IDL, LDL, HDL and Lp(a) are of particular interest as are apo-A-1 and II, apo-B and the apo-C and apo-E proteins. More than 40 awards study some aspect of lipoprotein formation, assembly, circulation, cell binding and degradation. About half that number of awards study the structure and function of apoproteins, including genetic variants. About ten of these studies involve molecular genetics, gene expression and mapping. A similar number of awards are concerned with cell-lipoprotein interactions (monocyte macrophage, vascular smooth muscle cells and endothelium) involving high affinity receptor pathways or scavenger endocytosis leading to intracellular lipid accumulation in atherosclerotic lesions or to lipoprotein degradation.

The recent elucidation at the molecular and cellular level of the receptor mediated pathway for cholesterol homeostasis by Brown and Goldstein has given an impetus to the study of receptors for normal and abnormal lipoproteins and the interaction between receptor proteins and apoproteins. It has also stimulated a renewed research activity on HMG CoA and its expression since it is a limiting enzyme for the synthesis of cholesterol.

Marine oils (n-3) in the diet tend to lower triglyceridemia, to lower LDL and raise HDL. They also tend to reduce blood platelet counts and affect bleeding time and perhaps thrombosis. Substrate competition between long chain n-3 and n-6 fatty acids also affects prostanoid metabolism with implications for thrombosis and also for leukotriene metabolism. Because of these properties the Institute currently supports some eight grants and expects to solicit a similar number for support in FY 1987.

Total extramural research support by NHLBI in FY 1985 in these areas amounted to 184 projects at an estimated cost of $37,507,000.

In addition, the NHLBI supports a major intramural research effort on lipid metabolism in its Molecular Diseases Branch. The overall objective of the research program of the Molecular Disease Branch is the delineation of the molecular and structural properties of the human plasma apolipoproteins, the physiological role of the apoliproteins and lipoproteins in lipid transport, the determination of the mechanisms involved in the regulation of cellular cholesterol metabolism and transport, and the elucidation of the metabolic and molecular mechanisms involved in plasma lipoprotein synthesis, transport, and catabolism in normal individuals and patients with disorders of lipid metabolism and atherosclerosis.

Nutrition

The Division of Lung Diseases (DLD) supports research on lung surfactant as this may be influenced by carbohydrate and by cholesterol metabolism, by fatty acid metabolism, and by dietary choline. There are also studies on lung protein turnover and on impairment of cell mediated immunity in severe

protein/calorie deficiency. The effect of Zn and Cu nutrition on free radical and oxidation events in the lung is under investigation as is the vitamin E content of the lung in various conditions.

The Institute also supports studies of vitamin E in oxidant damage to vessels in diabetes, as an inhibitor of platelet adhesion, and its deficient state in abetalipoproteinemia and cholestatic liver disease. Zinc and copper nutrition are also being studied for effects on serum lipids, on cholesterol absorption from the gut, and on cell membrane receptor behavior in cells such as blood platelets and adipocytes.

The Division of Blood Diseases and Resources supports some five grants concerned with vitamins D or K and coagulation and there are a small number of grants concerned with iron metabolism.

In contrast to the nutritionally oriented mechanistic studies noted above, the Division of Epidemiology and Clinical Applications supports many population-based studies of nutritional or metabolic nature that are directed at risk factors for cardiovascular disease. In this respect it may be noted that the Division supports twenty-three fellows in Preventive Cardiology. It is the responsibility of such fellows to develop and teach a suitable curriculum of preventive medicine in cardiology including prudent nutrition to undergraduates and post graduates at their institutions.

Currently there are some twenty-six awards for studies of the epidemiology of cardiovascular disease that include components of nutrition and risk factor metabolism. In twenty-five awards risk factor reduction is the object of research. Some studies are at work sites, others at schools or with other cohorts. An additional nine awards deal with obesity as a risk factor and its control. One study deals with patterns of alcohol use. Diet and exercise are under study in seven more awards. The relation of sodium intake to blood pressure in populations is the object of considerable activity. There are eight epidemiologic studies, three that involve potassium and three that involve sodium metabolism and stress. In seven studies there are interventions to reduce dietary sodium and in eight studies the objective is to prevent the onset of hypertension by sodium restrictions and various dietary and non-pharmacological means.

Total nutrition research supported by NHLBI in FY 1985 amounted to 324 projects with an estimated cost of $45,689,000.

Red Blood Cell Membrane and Enzyme Systems

Research is supported to elucidate the structure, function, and rheologic properties of the erythrocyte membrane in health and in congenital and acquired hemolytic disorders. The metabolic and transport systems of the erythrocyte in health and disease are included. In fiscal year 1985, the red cell membrane and enzyme system subprogram included 36 individual project grants and one SBIR grant and provided $7,344,000 in support. There were 7 research training and career development awards in this area for approximately $293,000.

Hematopoiesis and Stem Cell Kinetics

The goal of this research program is to develop a better understanding of normal cellular proliferation at the molecular and cellular levels, with emphasis on erythropoiesis and to apply the knowledge of normal cellular proliferation to diseases of abnormal bone marrow function with the specific aim of prevention, diagnosis, and treatment of non-neoplastic hematopoietic disorders.

In fiscal year 1985, the growing program in erythropoiesis and stem cell kinetics provided $3,059,000 to 18 individual research and program projects and $214,000 to 6 research training and career development awardees.

Cooley's Anemia and Other Hemoglobin Variants

This program provides support for the structure and function of hemoglobin and the globin genes in health and in the various hemoglobinopathies. Improved techniques for the prevention, diagnosis, and treatment of the thalassemia disorders are developed with particular emphasis on Cooley's anemia.

In fiscal year 1985, the program on Cooley's anemia and related hemoglobin variants included 42 individual research project awards and one Program Project grant for about $6,299,000. There were also 8 research training and career development awards for about $267,000.

Treatment of Hemoglobinopathies

The NHLBI intramural research programs provide a strong research base in the pathophysiology and treatment of hemoglobinopathies and other hematologic disorders. In fiscal year 1985, the Clinical Hematology Branch supported 16 projects on regulation of hemoglobin synthesis, bone marrow failure, chelation therapy for iron overload, and related topics.

Research conducted by the Laboratory of Molecular Hematology included work in gene regulation and gene transfer. These two NHLBI intramural research groups are at the forefront in the development of pharmacologic and genetic treatments of hemoglobinopathies.

Sickle Cell Disease

The Sickle Cell Disease program develops and support activities designed to reduce the morbidity and mortality from sickle cell disease through research and development, at both the fundamental and clinical levels; programs in screening, counseling, and improved management of patients with sickle cell anemia; and programs to educate the community and medical and allied health professionals.

The Sickle Cell Disease program supported 2 program project grants, 10 centers, and 37 individual research project grants totaling $22,158,000 in FY 1985. Three research career development awards in this area provided $143,000 in support. The Cooperative Study of Sickle Cell Disease, a multicenter study to develop data on the natural history of sickle cell

disease, comprises 18 research contracts and 2 interagency agreements that summed to $4,945,000 in FY 1985.

Other Research on Blood Disorders

In the general red cell area in fiscal year 1985, there were 1 Program Project grant ($978,000), 1 SBIR Phase II grant ($154,000), and 21 research training and career development grants ($2,731,000).

Along with its programs on red blood cell disorders and sickle cell disease, the NHLBI has consistently supported research in stem cell development and its growth factors and established a special program to provide purified erythropoietin to research investigators. In fiscal year 1983, special grant programs on aplastic anemia and on megakaryocytopoiesis were initiated. The megakaryocytopoiesis program has expanded and included 14 grants ($1,785,000) in fiscal year 1985.

In fiscal year 1986 the Institute will add to this portfolio up to 5 awards ($800,000) on the regulation of the B-globin gene, another 5 or 6 awards ($800,000) on the bleeding disorder in renal failure, and a Program Project grant on bone marrow transplantation (about $1,092,000).

In addition to the preceding topics, the NHLBI has primary interest in thrombosis or hemorrhage related to specific disease states, such as uremia, and in the synthesis or development of hemostatic components, including megakaryocytes. Through the Blood Resources Program, NHLBI fosters research on strategies to improve bone marrow donor recruitment and methods to preserve bone marrow for bone marrow transplantation.

In total, the Division of Blood Diseases and Resources supported 208 grants and 20 contracts and interagency agreements in these areas at a cost of $50,271,000 in fiscal year 1985.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive trait that is characterized largely by pancreatic insufficiency and chronic obstructive pulmonary disease with attending bronchial infection. The goal of the research program sponsored by NHLBI is to study the pulmonary involvement, which is the underlying cause of death in over 90 percent of cases.

In fiscal year 1985, the program provided 32 individual research grants and program projects for $4,178,362. The major emphasis of the program is to examine the abnormality in mucous synthesis and secretion, and the airway obstruction that results from mucous abnormalities. Studies are also supported to search for mechanisms of the defect in CF that lead to the pulmonary abnormality; identify genetic markers isolated from homo- and heterozygotes; and develop programs on health education and patient management.

Tenth Report of the Director
National Heart, Lung, and Blood Institute

Volume 3.
Lung Diseases

U.S. Department of Health
and Human Services
Public Health Service
National Institutes of Health

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive trait that is characterized largely by pancreatic insufficiency and chronic obstructive pulmonary disease with attending bronchial infection. The most significant component is the pulmonary involvement, which is also the underlying cause of death in over 90 percent of cases. The mechanism of the defect is not yet known. A diagnosis is made by an identification of the major clinical manifestations, a recognition of a family history of the disease, and a detection of elevated levels of chloride in the sweat. Treatment is empirical

and symptomatic. Despite the lack of specific and direct treatment, the average predicted life expectancy has been increased, but it is still only 20 years. In 1981, over 30,000 cases were recognized in the United States alone.

State of Knowledge in 1972

In 1972, cystic fibrosis was recognized as a recessive trait and was known to occur in approximately 1 in 2,000 Caucasian births in the United States and northern European countries. While the diagnosis could be made routinely by determinations of chloride levels in sweat, there was no way to detect carriers of the defective gene or to make a prenatal diagnosis. Prior to 1972, most work concerning the pathogenesis of CF related to exocrine gland dysfunction. Extensive but not very sophisticated studies of glycoproteins had indicated an abnormality of sugar composition, namely of increased ratio of fucose to sialic acid. While this abnormality was thought to contribute to abnormal physical properties of these glycoproteins and mucus, the observation could not be confirmed by all investigators. Considerable attention had focused on the role of interactions of calcium and glycoproteins and on subsequent alterations of CF mucus that contained excessive amounts of calcium. The relationship between this interaction and mucous abnormalities, however, was not delineated. Studies of sweat gland function had determined that the primary secretory fluid was normal and that the high content of sodium and chloride in excreted sweat was due to inhibition of reabsorption of sodium as the primary fluid was being transported along the secretory duct. Studies in the late 1960's and early 1970's indicated that a factor present in saliva and sweat of patients with CF was able to block sodium reabsorption by sweat gland ducts. Despite all attempts, this factor could not be isolated because of its lability and apparently unusual properties. Other studies suggested that alterations in autonomic regulatory function might contribute to the hypersecretory phenomenon characteristic of CF. Specific abnormalities, however, were not consistently defined.

Other observers had recognized that chronic lung infection is a major pathogenic factor in CF and that Staphylococcus aureus and Pseudomona aeruginosa are the major pathogens in the tracheobronchial tract. It was further recognized that the mucoid pseudomonas is characteristic, if not unique, for cystic fibrosis. Nutrition was considered a clinical problem unrelated to the basic pathophysiology of the disease.

New research directions were stimulated by the observation that CF serum contained an activity that inhibited ciliary motility. Attempts to use this activity to identify the CF gene

proved to be unsuccessful because the tests were either difficult to reproduce or not specific for cystic fibrosis.

Clinical studies had largely been focused on the treatment of pulmonary infection of obstructive lung disease. New and effective antipseudomonas antimicrobials in the form of gentamycin and carbenicillin had been introduced and proved to be superior to previous agents. Studies of the efficacy of therapy indicated that mist tents probably did not contribute substantially to the well-being of most patients.

Program Goals Through 1982

- Identify cystic fibrosis factors in patients and genetic markers in heterozygous carriers of the cystic fibrosis gene.
- Elucidate normal mechanisms involved in mucociliary clearance, and determine how these are modified in cystic fibrosis.
- Develop therapies and procedures for management of patients with cystic fibrosis.

Accomplishments Through 1982

A large number of studies have appeared concerning the etiology and pathogenesis of cystic fibrosis. While none has pinpointed what appears to be the mechanism of the defect, major breakthroughs have occurred in the basic understanding of the normal regulation of the airway structures that are involved in the secretory process, and technologic advances make it possible to study diseased tissue.

The major abnormality in CF is in mucous synthesis or secretion. Thus, considerable emphasis has been placed on the observation that mucus from the respiratory tract, intestinal tract, and uterine cervix is relatively dehydrated compared to mucus from normal individuals. In the lung, abnormalities of mucus result in airway obstruction, which is the usual cause of death in CF. Secretion from glands and surface cells of the airway combine with water to form the airway secretions, which are moved up the airway to the mouth by sweeping action of the cilia. Understanding the abnormalities in CF requires understanding of normal regulation of mucous secretion, water movement, and ciliary motion. A decade ago, little was known in these areas, but major

progress has been made through multidisciplinary approaches and several technical breakthroughs.

Since water makes up most of the airway secretions, the regulation of water is of utmost importance. Techniques used in other epithelia (for example: gut and kidney) have recently been applied to the airways. These studies have shown that water movement in the airways is controlled by a "pump" that actively moves ions across the airway surfaces; water follows passively. Methods have been developed to measure the minute volumes of water that are secreted. Some evidence suggests that abnormalities in ion transport may be an underlying mechanism in the pathogenesis of CF. In fact, the abnormalities in sweat secretion are used to diagnose the disease. Microtechniques are now being used in animal models of disease and in human tissue to explore possible abnormalities in the ion transport. Circulating factors may prevent the operation of normal ion pumps, or the cells themselves may lack normal pumps.

Most airway mucous secretions are derived from the submucosal glands. Again, multidisciplinary research has begun to identify the mechanisms by which humoral mediators and drugs regulate secretions. Glands contain serous cells and mucous cells. The first are believed to produce thin, watery secretions, and the second are believed to produce thick secretions. Recent studies have suggested that the functions of these two cell types are controlled separately. Major headway has also occurred in identifying the chemical nature and the determinants of the physical properties of mucus. Studies have indicated that mucous glycoproteins are more than normally sulfated in CF, and the abnormality is accompanied by increased average lengths of the oligosaccharide chains on these glycoproteins. The clinical implication of these abnormalities needs further exploration.

Cilia must beat in a specific, coordinated fashion to move a stream of liquid and to clear mucus. The filamentous structure of cilia has recently been discovered, and the power supply for ciliary motion has been shown. In patients with CF, a number of circulating factors have been reported. Each factor has been examined, and a number of biologic activities have been suggested, but none of the factors has been adequately purified or shown to be related to the genetic defect in CF. These factors include the ciliary inhibitory factor, which inhibits glycoprotein-debranching enzyme; a lectin-like activity, which promotes release of mucus from ciliated epithelium; and a substance with isoelectric focusing band at pH 8.4. Attempts to apply these observations to the identification of CF heterozygotes have met with only limited success, largely because of wide variability of response and overlap between the responses generated by homozygote, heterozygote, and control populations. None of these tests as yet has proven capable of consistently identifying CF in utero.

Efforts have been made to study mechanisms that lead to lung infection in cystic fibrosis. Abnormalities of pulmonary alveolar macrophages and lymphocyte defense systems occur, but they appear to be secondary to lung infection. So far, research has not found immunologic deficits. The function of the pancreas in lung abnormalities has been investigated, and it has been found that the "cystic fibrosis syndrome" is not dependent on the state of exocrine pancreatic function, as was once suggested.

Biochemical studies have suggested abnormalities in specific enzyme function (for example: protease activity and protease inhibitor), and mitochondrial dysfunction relating to intracellular distribution of calcium has been reported; but these studies have so far not provided specific insights into the pathogenesis of the disease.

Because of the difficulty of studying tissues from patients with CF, considerable effort has been exerted in developing an animal model of the disease. Thus far, no genetic model has been found, and none of the "induced" models mimic the cystic fibrosis clinical syndrome. Nevertheless, several forms of pharmacologic intervention have provided important clues concerning the modification of normal structure and function.

State of Knowledge in 1982

A considerable amount of information has been generated in a 10-year period concerning cystic fibrosis. The mechanism of the defect, however, remains unknown, and means to identify the CF gene in utero is yet to be developed. Research on the pathophysiology and pathogenesis of the disease seems unfocused, largely because of an inability to identify abnormalities that can be readily related to the clinical syndrome. In addition, it is difficult to eliminate from studies secondary effects of chronic lung disease and nutritional deficiencies. Lack of an adequate animal model has further precluded rapid advances.

Applied research has also been relatively slow in CF. Attempts to launch collaborative, large-scale studies of the various therapeutic modalities have been unsuccessful. New antibiotics have been developed, and more effective delivery of supplementary pancreatic enzyme has been engineered. Treatment, however, remains essentially the same as it was in 1972. Implication of hypersensitivity reactions in the pathogenesis of CF lung disease has opened new avenues of inquiry.

Program Goals 1982 to 1987

The long-range goals in CF research are:

- Search for mechanisms of the defect of CF that lead to pulmonary abnormality.
- Identify genetic markers for cystic fibrosis.
- Improve the care of patients that will enable them to lead a longer and better quality life.

Research Activities 1982 to 1987

The following activities are given as examples:

Basic Studies

- Attempt to characterize the basic science of metabolic defects centering on the function of cell membranes in affected secretory tissues: water and ion transport, biosynthesis and composition of mucus, and intracellular secretion and its control (cAMP and calmodulin). (See also research activities for nonventilatory functions of the respiratory system, page 76.)
- Identify genetic markers such as specific cell components that can be quantified in cells isolated from homo- and heterozygotes.

Clinical Studies and Patient Care

- Promote the availability of specific and sensitive lung function tests for early detection of impairment.
- Investigate means to combat pseudomonas infection effectively: better antibiotics and better modes of delivery of antibiotics directly to the affected area of the lung.
- Improve the delivery of oxygen during acute episodes of lung impairment.
- Identify and evaluate new and improved mucolytic agents.
- Investigate the relationship between nutrition and degree of respiratory impairment.

- Conduct prospective evaluation of CF patients to compare morbidity and mortality in males and females.

APPENDIX 3
NCI Activities Which Relate to NIDDK

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Cancer Institute

Memorandum

Date May 30, 1986

From Acting Chief, Planning and Analysis Branch, DCBD, NCI

Subject Administrative Review of the Programs of NIDDK

To Thomas E. Malone, Ph.D.
Deputy Director, NIH

The National Cancer Institute supports a broad range of studies designed to find improved methods of detection, diagnosis, treatment, and prevention of cancer, including cancers of the gastrointestinal tract and kidneys. This includes research performed in the intramural laboratories of the Institute as well as research grants and contracts funded by the NCI Extramural Research Programs. A summary of areas of common interest to the Extramural Program of NIADDK and the NCI is attached. A brief description of scientific activities that relate to programs of NIDDK and are conducted in the intramural Epidemiology and Biostatistics Program, Division of Cancer Etiology, is also provided.

Dr. Alan Rabson, who is a member of your committee, will make an oral presentation on the relevant NCI programs at your July 1-2 meeting.

Susan J. Ficker

Susan J. Ficker

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Cancer Institute

Memorandum

Date May 28, 1986

From Associate Director , ERP, DCBD, NCI

Subject NCI Activities which Relate to NIDDK

To Director, DCBD, NCI

The NCI has a number of extramural programs which border on or relate to the programs of NIDDK. Excerpts are attached from the most recent grant referral guidelines which identify areas of common interest to NIADDK and the NCI. To briefly summarize, these areas are as follows:

(1) Effects of sunlight radiation on cell biology.

(2) Studies of pigmentary metabolism as related to melanomas.

(3) Studies of bone and connective tissue related to the development and spread of bone tumors.

(4) Studies of various growth factors, hormones and their receptors in neoplasia (e.g., EGF, tranferrin, insulin).

(5) Studies of hepatitis virus in the etiology of hepatomas.

(6) Studies of bladder, prostate, endocrine and gastrointestinal dysplasias, hyperplasias and neoplasias.

(7) Nutritional studies related to cancer.

(8) Studies of hematopoietic and myeloid differentiation as they relate to neoplastic diseases of the blood-forming tissues.

(9) Bone marrow transplantation as it relates to cancer.

Brian

Brian W. Kimes, Ph.D.

Attachments

EXCERPTS FROM NCI REFERRAL GUIDELINES

The NCI should receive a primary assignment when the research deals with biological agents (viruses) as possible etiologic factors or cofactors in cancer and on the control of these agents and their associated diseases. CA assignment should be made when emphasis is placed on viruses, viral products, and related cellular substances such as tumor inducing agents or resulting antibodies; appropriate studies include biological, biochemical, molecular, immunological and physical investigations of actual, potential or suspected oncogenic viruses and their interaction with, and effects on their hosts, at all levels of biological organization.

AI - AI should be given primary assignment in virology when the research is directed solely at the etiology/elucidation/description of infectious diseases. Studies involving viruses which deal with their known or suspected potential for oncogenic sequelae in animals or man (e.g., retroviruses, HTLV-I, II, III, hepatitis B virus, papillomaviruses, herpesviruses, non-A/non-B hepatitis viruses) should be given primary CA assignment.

AM - AM should be given primary assignment in studies of hepatitis/cirrhosis when the research is directed at studies of liver enzymes/liver function as a result of the disease. Studies on the oncogenic sequelae of hepatitis/cirrhosis should be given primary CA assignment.

GM - All studies on the molecular or genetic mechanisms of carcinogenesis/oncogenesis/transformation in higher vertebrate systems relevant to NCI should be given CA primary assignment. Basic studies in model systems such as lower vertebrates, invertebrates, and plants should be given a GM primary assignment.

Studies on transforming DNA, virus integration or oncogenic virus gene regulation, when they relate to carcinogenesis, should be given primary CA assignments. Studies which emphasize a comparison of cellular processes in normal and neoplastic cells should be assigned CA primary, GM secondary. When studies of normal cells focus on cell growth regulation, cell differentiation, and cell cycle, they should be given GM primary and CA secondary assignments. These would include studies of growth factors, differentiation factors, lymphokines and cytokines which do not emphasize immune function. When immune function is emphasized, the primary assignment should be either CA or AI.

NS - Neuropathologic diseases caused by neurotropic tumor viruses such as the human papova viruses (e.g., JC virus) and wild mouse retrovirus; primary assignment should be given to NS if studies involve primarily the disease and pathology of disease. CA should be given primary assignment if the studies involve viral oncogenesis.

NCI should receive a primary assignment when the research is concerned with the induction, promotion, progression and prevention of carcinogenesis initiated by chemical or physical agents.

ES - ES should be given primary assignment when the study deals with chemicals in the environment and the environmental hazards of chemical and physical agents. The screening for potential carcinogenic agents is also appropriate. CA and ES should be given dual assignment for studies to develop carcinogenicity/mutagenicity test systems with CA primary when more basic mechanisms of carcinogenesis/mutagenesis are involved. CA should be given primary assignment when the study deals with the metabolism and mechanism of action of carcinogens of environmental interest.

GM - GM should be given primary assignment when the study deals with chemical and physical interactions of macromolecules with chemical agents, DNA replication and repair, mutagenesis, or drug metabolism and the study has a general biological focus. CA and GM should be given dual assignment with CA secondary for the above types of studies when there are components in which carcinogens are used or when mechanisms of carcinogenesis is a part of the study.

NCI should receive a primary assignment when the research involves studies of immunology directly related to host resistance and/or response to cancer and/or cancer therapy. NCI also supports basic research in immunology when the immunologic mechanism is considered to play a role in host resistance to cancer.

AI - CA and AI should be given dual assignment, with AI primary, in areas of immunology most relevant to infectious disease and allergy; e.g., B cell function, antibody structure and function.

CA and AI should be given dual assignment, with CA primary, in those areas considered to play a role in rejection of tumors, e.g., natural killer cells, cytotoxic T-cells, tumoricidal macrophages.

Other studies of basic immunology should be dually assigned to CA and AI, with primary assignment based upon the significance, aims and objectives of the study and/or patient population being used; e.g., immunologic aspects of bone marrow transplantation for leukemia vs. immunodeficiency, immunological aspects of hematopoiesis.

AM/HL - Studies of hematopoiesis should be dually assigned to CA and AI when the emphasis is on differentiation of lymphoid cells and development of immunologic function, especially when relevant to bone marrow transplantation. Basic hematology should be assigned to AM or HL as appropriate.

GM - Studies of basic cell biology, using cells of the immune system as a model, are appropriately assigned to GM. However, when these studies are related to development of immunologic reactivity, AI/CA or CA/AI assignment is appropriate.

As immunology research is relevant to the mission of several institutions, and the NCI supports basic research in immunology, CA secondary assignments are to be given when no other categorical assignment is appropriate.

The NCI should have primary assignment on grants dealing with the biology, biochemistry, genetics or molecular biology of tumor cells or tumor cell products.

NS - Primary assignment sould be given to the NCI for all studies of tumors of the nervous system when the emphasis is on understanding the biology and genetics of the cancer process. NS should receive secondary assignments. When tumor cells are used as model systems for understanding normal neural function, NS should receive primary assignment and CA secondary assignment.

HL/AM - Any study of the biology of lymphoma or leukemia cells, subcellular components or factors produced by the cells should be given NCI primary.

AM/GM - The NCI has broad interest in growth factors and peptide and steroid hormones and their effect on cell division, growth and cell movement or migration. When the study uses a tumor cell system, NCI should be given primary. When other target cell systems are used that may be related to cancer, NCI should be secondary.

EY - Dual assignments should be made on studies of primary tumors of the eye or visual system, including research on the biology, genetics, or diagnosis of retinoblastoma and ocular melanoma. The NEI should receive primary assignment in research projects that may lead to a better understanding of normal visual system development of function and to means of preserving vision in these disorders. The NCI should receive primary assignment when the main emphasis is on more general biological properties of tumors (e.g., metastasis, angiogenesis, neovascularization, etc.).

GM - When a study emphasizes the biochemistry, genetics, molecular biology or cell biology of a cancer cell or tissue it should be NCI primary. Studies utilizing a cancer cell line with the obvious intent to investigate a normal process should receive NCI secondaries.

HD - Projects using teratocarcinoma or teratoma cells to study differentiation and neoplasia should be given NCI primaries. If these cells are used as a model system for normal embryonic development the study should be given an NCI secondary.

The integration and function of genes related to cancer in blastocysts, transgenic embryos and mice and chimeric mice should be given NCI primary.

AG - Any tumor cell study when the emphasis is on understanding the cancer process should be given NCI primary.

The NCI should receive primary assignment of applications proposing research in all areas of preclinical and clinical cancer treatment. Primary assignment to NCI therefore includes proposals to study chemotherapy, radiotherapy, biological response modifiers, and surgery as treatments for cancer. In addition, the NCI supports research in all aspects of diagnostic imaging.

AG - Cancer in the elderly. NCI should receive primary assignment when the emphasis is on elderly populations' response to and tolerance of cancer treatment. Studies on how the aging process may be affected by cancer or cancer treatment would be assigned to AG as primary.

EXCERPTS FROM NIADDK REFERRAL GUIDELINES

- Experimentation in dermatologic drugs

  All grants for the development of drugs to be used in skin diseases should receive AM primaries. The development of drugs to be administered transcutaneously for the treatment of diseases other than skin disease may receive primary assignments to the most appropriate Institute and a secondary assignment to AM if the thrust of the research is the effect on the disease of the other organ. However, if the thrust of the research is the transcutaneous absorption or penetration of the new drug rather than its systemic effect, the primary assignment should be to AM.

- Allergic contact and primary irritant types of dermatitis

AI - All grants whose major thrust is the investigation of allergic contact and primary irritant reactions in the skin should receive AM primaries. If the thrust of the grant is the mechanism of delayed hypersensitivity or primary irritation in a general sense and the skin is used only as one of several organ systems to be investigated or as a model, AI may be the primary with AM as secondary.

- Bullous diseases of skin (pemphigus, pemphigoid, dermatitis herpetiformis, epidermolysis bullosa)

AI/HD - All investigations of these diseases should receive AM primaries. In those instances in which the pathogenesis is felt to be on an immunologic basis, AI may receive a secondary. In those cases where the pathogenesis is genetic, HD may receive a secondary. In those instances in which the bullous disease is a multisystem disease with skin only one of many organ systems involved, and not the primary organ affected, the most appropriate Institute may receive primary designation with AM secondary.

- Diseases of supporting tissue of skin (scleroderma, discoid and systemic lupus erythematosus)

  All such investigations should receive AM primaries. If the disease to be studied is a multisystem disease affecting skin along with other organ systems, and the investigation is of a more basic nature, the most appropriate Institute may receive a primary assignment with AM secondary. However, if the investigation of a multisystem disease concentrates on the skin disease aspect, AM should receive primary assignment.

- Deleterious effects of sunlight (photobiology, porphyrias)

CA - All such investigations should receive AM primaries except for investigations of skin cancer in which sunlight is only one of several potential etiologyic agents being investigated as part of the induction of skin cancer. In that case, CA may be primary with AM secondary.

- Atopy and other genetic and congenital skin diseases

AI/HD - All such studies of these diseases where the concentration is on the skin disease should be AM primaries. Those diseases thought to be on an immunologic basis should carry AI secondaries and those genetic diseases carry HD secondaries. In those cases where the major thrust of the investigation is on the basic underlying process, be it immunologic or genetic, and the skin disease is only one organ system to be studied among many, AI or HD may receive the primary designation with AM secondary.

- Vitiligo and other disorders of pigmentation

CA - All studies of vitiligo and non-malignant pigmentary disorders should receive AM primaries. Investigations of melanoma that also involve the relationship of vitiligo to melanoma should receive either AM or CA primaries, depending upon the major thrust of the grant. Those investigations with major thrust into melanoma should receive CA primary designations with AM secondary. All others should receive AM primary assignment.

- Burns, wound healing and granuloma formation

GM - Burns and wound healing, particularly the development of artificial skin, may receive GM primary designations when the thrust of the application is the basic investigation of the healing process or artificial skin. However, when the basic thrust of the grant is structure and function of skin, AM primary designation is appropriate.

IV. Bone Diseases and Disorders

- Acquired Bone Diseases

In general, studies and diseases in which bone is the target organ should receive AM primaries. Some examples are osteomalacia, osteodystrophy and Paget's disease.

AC - Osteoporosis is a slowly developing condition that initiates at about age 35. Studies on osteoporosis as focused primarily on

understanding bone metabolism should be AM primary. AG should receive primary assignment when the emphasis is on the contribution of age-related changes to osteoporosis. In all cases osteoporosis-related grants should receive a dual assignment between AM and AG.

- Spine Disorders

HD/NS - As related to the bone (vertebrae) and connective tissue (disc, ligaments, tendons, etc.) studies on spinal disorders are primarily AM. When the major effort is directed to nerve tissue, the assignment should be NS primary. Dual assignments are appropriate for most cases. A developmental disorder such as scoliosis is typically AM primary with the exception of generalized disease studies that may be HD primary.

V. Muscle and Musculoskeletal Diseases and Disorders

- Repair of Injuries and Diseases

AG/AI/CA In general, studies on repairs and treatment of bone and connective tissue are AM primary, unless specifically oriented toward the aging process or elderly, in which case they should be AG primary. Treatment methods range broadly including exercise, drug therapy, surgical intervention, and bone and cartilage transplantation. Investigation on bone tumors, their development and spread are CA primary. Bone transplantation investigations related to a general study of immunology of transplants should be assigned AI/AM.

- Devices

DE/GM - Studies on prosthetic joints and connective tissue replacement (including design, functional analysis, biomaterials, and attachment) are AM primary. Specific studies related to the mouth areas are DE primary. General studies of biomaterials are GM primary.

- Muscle Diseases

NS - AM has primary interest in the diseases and disorders of skeletal muscle. This includes myopathies, myotonia, and the muscle dystrophies. The pathophysiology of these conditions, including studies on changes in muscle function, structure or proteins, should be assigned to AM. Studies on neural dysfunction, or neural etiology of the conditions may be NS primary; however, AM has primary interest in studies on the internal changes of muscle if a nerve is severed or atrophied.

GM - In general, AM is primary for muscle injury and regeneration, though studies looking at trauma to individuals, with a component on muscle, may be GM.

VI. Nature, Function, and Action of Hormones, Brain-Gut Peptides and Hormone-Like Agents

HD - In general, for studies in which the emphasis is on development, with endocrine effects being secondary, HD is primary. Where major emphasis is on the hormones and endocrine organs in various stages of the life cycle, AM is primary. For example, endocrinologic studies relating to fetal development are HD primary. General endocrine studies which may include fetus as well as other developmental stages are AM primary.

In studies of endocrine diseases in infancy, childhood and adolescence, AM is primary when the emphasis of the studies is on hyponormal, and hyperactivity of the adrenal, parathyroid, and thyroid. Studies of hypopituitary dwarfism are always AM primary; studies of other pituitary hormones and hypothalamic releasing factors are AM primary unless they relate specifically to studies of the reproductive system or reproduction, in which case they are HD primary. Developmental aspects of rates of production, release and actions of hormones, growth factors, etc., are HD primary if the emphasis is on development.

AG - General endocrine studies are AM primary, but age-related changes in endocrine function are AG primary.

AI - Immunological aspects of immunological diseases, including autoimmune endocrine diseases, are AI primary, except that the endocrine aspects of autoimmune disease are AM primary.

CA - Studies of growth factors, hormones, and receptors in cancer cell growth are CA primary when related to tumors, but are otherwise AM primary.

DE - Studies of the role of parathyroid hormone in relationship to teeth and jaws is DE primary; otherwise assign AM primary.

ES - Environmental effects on the endocrine system are ES primary.

GM - General receptor studies are GM primary unless emphasis is on hormone receptors, in which case AM is primary.

HL - Studies of the role of hormones in hypertension (e.g., adrenal mineralocorticoids, renin-angiotensin system) are HL primary, while other hormonal actions are AM primary.

NS - Studies of neuropeptides with an emphasis on CNS origin and action are NS primary; emphasis on the relationship to the endocrine system is AM primary.

VII. Insulin and Other Agents for Control of Blood Glucose

GM/HD - Assign AM primary when the focus of the application is on any aspect of glucose, carbohydrate, protein and lipid homeostasis or the hormones, cells, organs, drugs, or devices involved in such metabolic processes. This includes studies of the basic mechanisms of synthesis, secretion, degradation and action of insulin, glucagon and related peptides (growth factors). Assign HD primary if the focus of the application is on growth and development with a resultant secondary interest in metabolism. Assign to GM if the focus is on general mechanisms of enzyme regulation and uses metabolic pathways as examples.

VIII. Fundamental and Clinical Studies of Diabetes Mellitus

GM/HD - AM maintains a strong interest in all applications on any aspect of Diabetes Mellitus. Assign AM primary if the application focuses on the disease in any of its manifestations (etiology, prevention, treatment, pathophysiology). This would include animal models, behavioral/psychosocial studies and epidemiological investigations of diabetes and its complications. Assign HD primary if the study focuses on childhood or adolescent-limited aspects of diabetes mellitus. Assign to GM if the application merely uses diabetes mellitus as an example or model system to study some general phenomenon of genetics, cellular regulation or dysfunction.

* * * * *

GM - Assign AM primary if the focus of the application is on the genetics of Cystic Fibrosis, cloning of the CF gene, or therapy of the antecedents of CF; assign GM primary if the research focuses on a broad range of inherited diseases and CF is used as one of the models. Assign AM primary if the research focuses on the epidemiology of CF as an inherited metabolic disease; assign GM primary if the research focuses on a broad range of inherited diseases and CF is used as one of the models. Assign AM primary if the research focuses on the epidemiology of CF as an inherited metabolic disease; assign GM primary if the research is focused on genetic epidemiology, where general principles applicable to many diseases are involved.

HL - Assign AM primary if the application is on the pathologic and physiologic alterations of CF as a whole, where pulmonary complications are but one part of the study; assign HL primary when involvement of the lung is the primary focus. Assign AM primary if the research is focused on the development of new treatment modalities, diet therapies, coping strategies, or the evaluation of technologies and/or procedures directed at diagnosis or monitoring of CF patients; assign HL primary when the emphasis is on the lung involvement alone.

XIV. Structure and Function of the Exocrine Pancreas, Biliary Tract and Liver

HL - Studies on lipid regulation by the liver, via cholesterol-containing lipoproteins, of lipid output in the bile and on intestinal uptake of lipoproteins are AM primary; otherwise, studies of lipid regulation are HL primary.

XV. Diseases and Disorders of the Exocrine Pancreas, Biliary Tract and Liver, and Experimental Models

AI/CA/ HL	AM is primary on studies of non-viral hepatitis (acute and chronic) and on chronic liver diseases, cirrhosis, etc., that result from all types of hepatitis except alcoholic.

HL - Studies of hypertension, normally HL primary, are AM primary if specifically on portal hypertension. In studies of alpha-1-antitrypsin deficiency, HL is primary if the bronchopulmonary system is emphasized; if emphasis is on liver, AM is primary.

HD - Cholestasis associated with the perinatal period (20 weeks gestation through 28 days postnatal life) is HD primary. In periods beyond this (as in biliary atresia, Aligille's syndrome, Dubin Johnson, and Crigler-Najjar) are AM primary.

XVI. Fundamental and Clinical Studies of Nutrition and Malnutrition

CA/GM/HD — HD nutrition programs include nutrition as it relates to maternal and child health, nutritional factors in the growth and development of the fetus, child and adolescent, nutrition in adult development and aging, and obesity and body composition. In these cases, assignment should be based upon the intent of the research:

Studies in basic and clinical nutrition are of primary interest to AM; studies of nutrition in developmental processes are of primary interest to HD. Parenteral nutrition is generally of interest to AM except when directed toward problems of high risk and young infants, in which case it is of major interest to HD. Studies of nutrition related to cancer are CA primary. Studies relevant to trauma and burns should be GM primary.

XIX. Urological Diseases and Disorders

AG - Benign Prostatic Hyperplasia in the aged is AG primary. AM has primary interest in studies attempting to assess factors contributing to the onset and progression of the disease without reference to the aged; such studies would include cell biology, biochemical endocrinology, physiology, neurophysiology, developmental biology, and animal models.

AI - AI is primary on grants proposing to study urinary tract infections, except that AM is primary on grants assessing urinary tract infections, pyelonephritis and interstitial cystitis; especially of interest are studies of the structure and function of the urinary tract related to infection, pyelonephritis, reflux and/or other uropathies.

CA - CA is primary in assessments of bladder/prostate cancer. AM has primary interest in studies of the abnormal prostate, or bladder, wherein a cancerous prostate may simply provide a pathological control for the study of benign growths (e.g., Benign Prostatic Hyperplasia) or prostatitis.

HD - Studies on reproduction related to fertility/infertility and attendant factors are normally HD primary. AM is primary in assessment of impotency, specifically erectile dysfunction, resulting from disorders of the neural or vascular systems, and in therapeutic approaches to correct such disorders.

NS - NS is primary in studies assessing innervation of the bladder when the bladder simply provides an end-point for such investigations.

AM is primary in such studies when the goal of the research is to evaluate factors regulating bladder functioning, neurophysiological or neuropharmacological, wherein the primary aims are the understanding of how the bladder functions under normal and abnormal circumstances.

XX. Hematopoiesis and Factors Affecting its Control and Regulation

XXI. Hematologic Disorders and Therapeutic Modalities

HL - Molecular, genetic, biochemical, physiological and clinical studies related to the structure and function of hemoglobins and hemoglobin variants in Sickle Cell Disease, the Thalassemias and related disorders are HL primary. All aspects of hemoglobins and hemoglobin variants where related to general problems of genetic and molecular control of biosynthesis, or comparative studies of structure and function (other than as related to Sickle Cell Anemia and the Thalassemias) are AM primary. Studies of normal or abnormal hematopoietic stem cell development are AM primary. Studies directly related to aplastic anemia may be considered for HL primary assignment.

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Cancer Institute

Memorandum

Date May 29, 1986

From Administrative Officer, DCE, NCI

Subject Administrative Review of Program of NIDDK

To Acting Chief, Planning and Analysis Branch, DCBD, NCI

As per your request of May 21, I am attaching a list of DCE scientific activities that relate to the programs of NIDDK.

Mark F. Kochevar

Attachment

cc:
Dr. Adamson
Dr. Sieber
Ms. Topalian

Provided below is a brief description of scientific activities that relate to the programs of NIDDK and are conducted by the intramural staff of the Epidemiology and Biostatistics Program. These activities include studies in the environmental and occupational areas, as well as studies related to genetic susceptibility.

Digestive System Studies

An evaluation of a screening program among pattern makers for colorectal cancer and polyps found a 2.5-fold excess risk of colon cancer. Further analyses were unable to link the excess to any specific characteristic of pattern making.

Evidence from geographic studies of colorectal cancer suggests that the risk among migrants from high-risk northern areas of the U.S. to low-risk retirement areas in the south declines rapidly to the low southern rate. Initial analysis indicates that age at migration is key, with those under 45 at migration showing some decline in risk.

A case-control study of colorectal cancer is focusing on fecal mutagen level as a possible risk factor for this disease. Fecal mutagenicity and fecapentaene, a potent fecal mutagen, are being measured.

Among atomic bomb survivors, preliminary analyses indicate a strong dose-response relationship for colon cancer, especially the sigmoid colon, but none for rectal cancer.

A descriptive study revealed that colorectal cancer incidence and mortality rates for 1975-79 for Puerto Rican-born residents of New York City were about 2.0 times those for Puerto Ricans living in Puerto Rico, but less than those for other whites in New York City, suggesting that changes in lifestyle and environment may be involved in the higher rates in migrants. For stomach cancer, incidence rates for Puerto Rican born residents were slightly, but not significantly, higher than rates for those in Puerto Rico. In contrast, stomach cancer mortality rates for Puerto Rican residents of New York were lower than rates in Puerto Rico.

A collaborative case-control study of stomach cancer is being conducted to investigate reasons for the high risk of this cancer in parts of north and central Italy. Some provinces in this region have among the highest stomach cancer mortality rates in the world. The study will concentrate on dietary exposures, including the apparently high consumption of preserved meats in the high-risk areas.

As part of an effort to investigate associations between nutrition and cancer, a dietary questionnaire was part of a study of pancreatic and stomach cancers in southern Louisiana. The relative risk of stomach cancer in the high-risk area of southern Louisiana was inversely related to an index of vitamin C intake.

In collaboration with the People's Republic of China, case-control studies are being done in China to assess nutritional risk factors associated with esophageal and stomach cancer.

In a multi-center, population-based case-control study of oral cancer, nearly 1500 cases and 1500 controls will be enrolled. The study will evaluate the effects of smokeless tobacco (chewing tobacco and snuff), diet, electronics manufacturing and certain other occupational exposures, and mouthwash use. In another smokeless tobacco-related study, interviewing has been completed for a case-control study of esophageal cancer in coastal South Carolina.

A large-scale, population-based, interdisciplinary study of four tumor sites (esophagus, pancreas, prostate, and multiple myeloma) that are excessive in the black population is about to enter the field. A major focus of this investigation will be to assess nutritional risk factors, and to determine the extent to which these and other risk factors might explain the racial variation in the four tumor types.

A study is being done of liver cancer and hepatitis in veterans of World War II. Evidence has linked the hepatitis-B virus with an increased risk of hepatocellular carcinoma.

Field work has begun for a case-control study of biliary tract cancer in Los Angeles. Both bile duct and gallbladder cancer will be studied.

Kidney and Urogenital System

Analysis is being done on a large case-control study of renal cancer in Minneapolis-St. Paul. An association was found between renal pelvis cancer and long-term use of phenacetin and acetaminophen-containing analgesics. The link to acetaminophen was based on small numbers of cases, but is of concern in view of a report of its carcinogenicity in laboratory animals. To evaluate further the issue of analgesics and renal pelvis cancer, plans for a large multi-center case-control study are being developed.

A major study of bladder cancer found: (1) A decrease in risk associated with the cessation of smoking or with switching from unfiltered to filtered cigarettes; (2) A significant excess risk of 50 percent for males usually employed as truck drivers or delivery men; and (3) No excess risk for tuberculosis chemotherapy, principally isoniazid. Analyses of another study in high-risk areas of New England, suggested an increased bladder cancer risk associated with tobacco usage, truck driving, textile work, and leather work.

The genetic predisposition to a constellation of growth disorders is being studied, including adrenal and liver tumors. Genetic factors are also being studied in a family with multiple cases of renal cancer and in another family with Wilms' tumor.

Provided below is a brief description of scientific activities that relate to the programs of NIDDK and are supported by the extramural program of the Epidemiology and Biostatistics Program.

In the area of the digestive system, the extramural program supports nineteen grants. They include two studies of risk factors for cancers of the mouth or esophagus, with particular interest in alcohol and trace elements; two studies of gastric cancer risks, one of which is concerned with risk of cancer following

partial gastrectomy; an epidemiologic and a genetic study of colorectal polyps in relation to cancer of the colon; the support of a resource for hereditary non-polyposis colorectal cancer; five studies of colorectal cancer, investigating risks relating to prior cholecystectomy, vitamins and selenium, exercise, migration and dietary change, among other factors. Three other grants involve studies of anal cancer, focusing attention on the relationship to communicable agents. Two agents involve the influence of prior infection with hepatitis-B virus and risk of hepatoma. Two other grants are concerned with risk factors for biliary tract neoplasia.

The single grant in the area of urogenital cancer is concerned with the relationship between a genetic marker of metabolic capacity to modify chemical substance and bladder cancer risk.

APPENDIX 4
Grant Referral Process

Grant Referral Process

Assignment of Grant Applications to the NIDDK

WHO--One dozen GM-15 senior Health Scientist Administrators who, in addition to serving as Executive Secretaries, also work as Referral Officers for about 20 percent of their time.

WHAT--Annually these individuals, along with two assistant section chiefs, assign 33,000 PHS grant applications. Each application is assigned on the one hand to an Initial Review Group (study section), and on the other hand to a potential funding component, e.g., NIDDK. When more than one funding component has an interest in the subject of a grant application, multiple assignments are made.

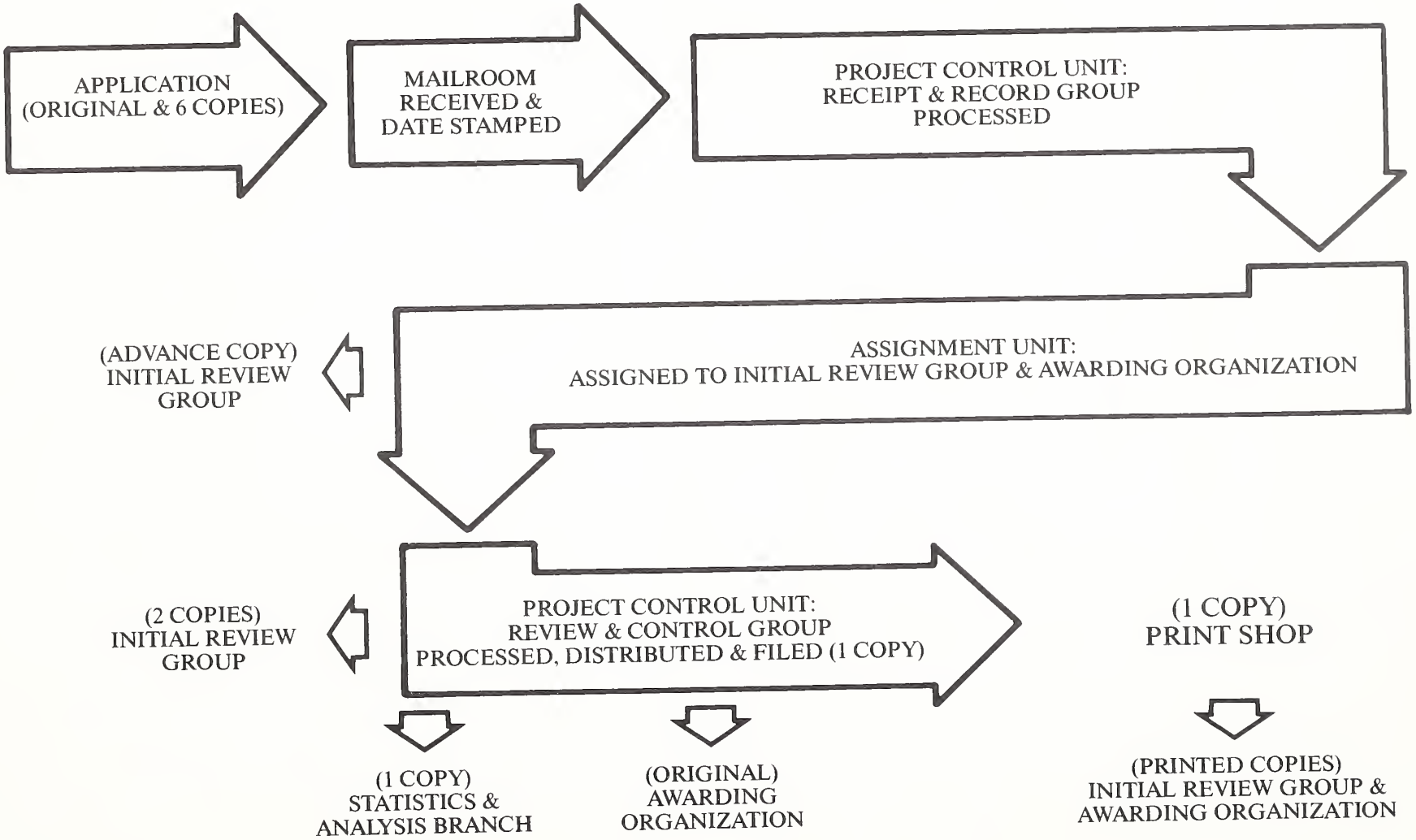
WHERE--The Assignment Unit of the Division of Research Grants is located in the Referral Section of the Referral and Review Branch. When making assignments, Referral Officers share a 900 sq. ft. room where they can interact freely with one another during their deliberations.

WHEN--The most active assignment periods are from mid-January to mid-April, from mid-May to mid-August, and from mid-September to mid-December.

WHY--Having one central receipt and referral point for the entire Public Health Service helps reduce confusion and redundancy. It also allows for an accountable, standardized, independent and impartial assignment of grant applications to study sections and funding components.

HOW--In making the so-called institute assignments, Referral Officers rely on the purple "Referral Guidelines for Funding Components of PHS." They pay special attention to the overlap sections. If the work proposed in a grant application represents a major programmatic interest of one institute and a minor interest of another, it is given dual assignment with the major institute listed as primary and the minor institute listed as secondary. When it comes to funding, primary assignees have first rights of refusal. If the work falls squarely within the territory of two institutes, the Referral Officers exercise their best judgement, keeping in mind the essence of the work and where it is likely to lead if successful. For most applications the process is straightforward and quick (N.B.: 12 Referral Officers, 33,000 applications, 20% effort). For some applications the procedure becomes interactive and consultative, with Referral Officers checking with colleagues in the Division of Research Grants and program directors in the institutes. Typically, in making an institute assignment, a Referral Officer will read the title of the application, the abstract on page two, and the specific aims. He or she will also read any correspondence submitted by the principal investigator or by NIH staff.

FLOW OF A COMPETING GRANT APPLICATION THROUGH THE DRG REFERRAL SECTION



APPENDIX B
Testimony of Public Witnesses

LIST OF ORGANIZATIONS PROVIDING TESTIMONY

*E. Darracott Vaughan, Jr., M.D.
Chairman Research Committee
American Urological Association

*Robert W. Schrier, M.D.
President
National Kidney Foundation, Inc.

Harley M. Dirks
President
Health and Medicine Counsel of Washington

*Jean G. Bacon
Executive Director
Polycystic Kidney Research Foundation

*Richard Cooper, M.D.
Chairman, Public Education Committee
American Society of Hematology

*Suzanne Rosenthal
National President
National Foundation for Illeitis and Colitis

Diane C. Coussan
President
Parent Council for Growth Normality

*John T. Farrar, M.D.
President
Digestive Diseases National Coalition

*James A. Olson, Ph.D.
President
American Institute of Nutrition

Sidney H. Ingbar
President
The Endocrine Society

*Russell Chesney, M.D.
President
Pediatric Nephrology Society and
President, Society of Pediatric Research

* Delivered oral presentation at July 1, 1986 public hearing.

Michael Di Filippo
Executive Director
Cooley's Anemia Foundation, Inc.

Robert K. Dresing
President and C.E.O.
Cystic Fibrosis Foundation

Pamela B. Davis, M.D., Ph.D.
Chief, Pediatric Pulmonary Division
Rainbow Babies' and Childrens' Hospital

Donald E. Wilson, M.D.
Chairman
National Digestive Diseases Advisory Board

Harold Rifkin, M.D.
President
American Diabetes Association, Inc.

SUMMARY-PUBLIC BRIEFING NIDDK - July 1,1986

The American Urological Association, The American Association of Clinical Urology and the Society of University Urologists make the following recommendations to NIDDK.

1. We support, in the strongest terms, the continuation of the Kidney, Urology and Hematology cluster as it now exists within NIDDK and as a visible sign of the importance of these areas within the institute we recommend that the new title of the institute be the National Institute of Diabetes, Digestive, Kidney, Urologic and Hematologic Diseases (NIDDKUH).

2. We strongly support the NIH report to the Congress requested in House Report 99-289, accompanying the appropriations bill which called for an evaluation of the proposal to establish up to six Kidney-Urology Research Centers. Particularly we support the NIH conclusion that one of the major goals of such a centers program would be to focus on benign prostatic hyperplasia (BPH). This is an area ready for considerably more research, as the disease affects the majority of men over the age of 60.

3. We support the recommendation of the Kleit committee that "the development of young broadly trained investigators with multi-disciplinary backgrounds are crucial to future research programs in Kidney/Urological diseases" and thus support the expansion of Training grants, "first awards" and clinical investigator's awards in Urology.

4. In response to the report of the Urology Research Coordinating Committee (March 1985) we strongly recommend expanded funding in the areas of benign prostatic hyperplasia (2.04 million FY 84), urinary tract infection including irritative diseases of the bladder especially in females (420 thousand FY 84) and neuropathic diseases of the urogenital system (259 thousand FY 84).

Respectfully submitted,

E. Darracott Vaughan, Jr., M.D.
Chairman, Research Committee
American Urological Association

EDV/m

DR. Vaughan

In behalf of the American Urological Association, the American Association of Clinical Urology and the Society of University Urologists, I would like to thank your committee for allowing me to speak to you today in behalf of the urological community and the patients we treat.

There is no doubt in our minds that funding for Urological Disease Research is "at home" if you will in NIDDK as a part of the kidney, urology, hematology program. In fact, as I will explain in a moment, NIDDK has taken a leadership role in identifying current funding directed towards urological diseases throughout NIH in an attempt to enhance coordinated activities.

However, first let me address the obvious, that is the link between kidney and urology. While urologic diseases extend beyond the kidney itself the anatomic, physiologic, and metabolic basis of both disciplines is the same. To give a few examples, the techniques which have resulted in genetic mapping for polycystic disease may also eventually be applied to other hereditary and congenital anomalies involving the entire urinary

tract.

Common immunologic mechanisms may underly the progressive renal failure sometimes seen following successful surgical treatment of reflux or medical treatment of pyelonephritis. The role of dietary protein restriction on progression of renal disease may be as important to the patient following uninephrectomy for the management of a variety of urological diseases as to the patient with diabetes or glomerulonephritis. I could continue beyond my alloted time.

In addition many entities are jointly studied and treated by nephrologists and urologists. Hence we are both interested in research concerning urolithiasis, pyelonephritis and infections involving the lower urinary tract, obstructive uropathy, congenital anomalies, acute renal failure and the wide subject of ESRD including renal transplantation.

One tangible evidence of the interaction is the activity of the Intersociety Group which led to the Report on an Evaluation of the Proposal to Establish Kidney and Urologic Diseases

Research Centers which was requested in House Report #99-289 by the Committee on Appropriations and was released February 1986. This study carefully carried out by NIADDK is well known to all of you so I will not review its contents except to state the conclusion.

"Based on an evaluation of these considerations, there is sufficient reason to believe that the proposed centers program is scientifically feasible and that it would contribute positively to advances in research knowledge and therapeutic approaches relative to ESRD and BPH. The NIH is therefore supportive of the concept of kidney and urologic diseases research centers, if additional resources were to be made available for this purpose."

This report is an excellent example of why kidney and urology should remain together within NIDDK.

Let me now return to address research in urologic disease per se especially in relationship to NIADDK. Three years ago, for the first time, as Chairman of the AUA Research Committee I began to testify before the House and Senate Appropriations Committees in behalf of Urological Research. It rapidly became clear that prior legislation did not carry urology in most places within NIDDK and in fact we realized that there was no clear tabulation of research directed towards urological disease

throughout NIH. Accordingly, The House Appropriations Committee Report #98-911, page 47 requested:

"The Committee requests that a urology research coordinating committee be formed which would consist of representatives from each NIH institute now involved in urology research, as well as representatives from the Veterans Administration and the Department of Defense, and any other Federal agency having urology research responsibilities. This committee would be under the leadership of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, which presently has an identified urology research program, so that Federal urology research activities can be better coordinated. Also, this committee should be charged with the task of compiling all Federal urology research efforts in all agencies, including specific grants and funding amounts, such compilation is to be completed prior to the fiscal year 1986 appropriations hearings."

In response, Dr. Charles Rogers, Urology Program Director, prepared a thorough review of all NIH and other federal funding directed towards Urological Disease for FY 84. Moreover, contact individuals were identified for all institutes and an Interagency Coordinating Committee on Urology was established. Clearly NIDDK and The Urology Program Director specifically have taken the leadership role in this effort.

On a broader scale, research against urologic disease is now perceived by Congress as a mandate of the NIDDK as is evident by the October 11, 1985 statement concerning the institute in the Congressional Record. I have appended their statement to this

report with the references to urology highlighted.

Looking to the future we feel that NIDDK is now aware that urologic diseases encompass more than the kidney as shown by the two workshops on benign prostatic hyperplasia and erectile dysfunction in the male. The institute should direct attention to basic research in all areas of urologic disease including infertility, erectile dysfunction, BPH, and inflammatory diseases of the bladder as well as the more traditional area of stone diseaes, obstruction and urinary tract infection.

Finally in urology there remains a dearth of both basic scientists and clinical investigators with the multi-disciplinary background critical to make basic research contributions toward the understanding of urological disease. Accordingly, we strongly support increased funding of training and support programs to produce and sustain new investigators in the discipline of Urology.

"Subpart 3—National Institute of Diabetes and Digestive and Kidney Diseases

"PURPOSE OF THE INSTITUTE

"SEC. 426. The general purpose of the National Institute of Diabetes and Digestive and Kidney Diseases (hereafter in this subpart referred to as the 'Institute') is the conduct and support of research, training, health information dissemination, and other programs with respect to diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and kidney, urologic, and hematologic diseases.

"DATA SYSTEMS AND INFORMATION CLEARINGHOUSES

"SEC. 427. (a) The Director of the Institute shall (1) establish the National Diabetes Data System for the collection, storage, analysis, retrieval, and dissemination of data derived from patient populations with diabetes, including, where possible, data involving general populations for the purpose of detection of individuals with a risk of developing diabetes, and (2) establish the National Diabetes Information Clearinghouse to facilitate and enhance knowledge and understanding of diabetes on the part of health professionals, patients, and the public through the effective dissemination of information.

"(b) The Director of the Institute shall (1) establish the National Digestive Diseases Data System for the collection, storage, analysis, retrieval, and dissemination of data derived from patient populations with digestive diseases, including, where possible, data involving general populations for the purpose of detection of individuals with a risk of developing digestive diseases, and (2) establish the National Digestive Diseases Information Clearinghouse to facilitate and enhance knowledge and understanding of digestive diseases on the part of health professionals, patients, and the public through the effective dissemination of information.

"(c) The Director of the Institute shall (1) establish the National Kidney and Urologic Diseases Data System for the collection, storage, analysis, retrieval, and dissemination of data derived from patient populations with kidney and urologic diseases, including, where possible, data involving general populations for the purpose of detection of individuals with a risk of developing kidney and urologic diseases and (2) establish the National Kidney and Urologic Diseases Information Clearinghouse to facilitate and enhance knowledge and understanding of kidney and urologic diseases on the part of health professionals, patients, and the public through the effective dissemination of information.

"DIVISION DIRECTORS FOR DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES, DIGESTIVE DISEASES AND NUTRITION, AND KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES

"SEC. 428. (a)(1) In the Institute there shall be a Division Director for Diabetes, Endocrinology, and Metabolic Diseases, a Division Director for Digestive Diseases and Nutrition, and a Division Director for Kidney, Urologic, and Hematologic Diseases. Such Division Directors, under the supervision of the Director of the Institute, shall be responsible for—

"(A) developing a coordinated plan (including recommendations for expenditures) for each of the national research institutes within the National Institutes of Health with respect to research and training concerning diabetes, endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases;

"(B) assessing the adequacy of management approaches for the activities within such institutes concerning such diseases and nutrition and developing improved approaches if needed;

"(C) monitoring and reviewing expenditures by such institutes concerning such diseases and nutrition; and

"(D) identifying research opportunities concerning such diseases and nutrition and recommending ways to utilize such opportunities.

"(2) The Director of the Institute shall transmit to the Director of NIH the plans, recommendations, and reviews of the Division Directors under subparagraphs (A) through (D) of paragraph (1) together with such comments and recommendations as the Director of the Institute determines appropriate.

"(b) The Director of the Institute, acting through the the Division Director for Diabetes, Endocrinology, and Metabolic Diseases, the Division Director for Digestive Diseases and Nutrition, and the Division Director for Kidney, Urologic, and Hematologic Diseases, shall—

"(1) carry out programs of support for research and training (other than training for which National Research Service Awards may be made under section 487) in the diagnosis, prevention, and treatment of diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and kidney, urologic, and hematolog-

ic diseases, including support for training in medical schools, graduate clinical training, graduate training in epidemiology, epidemiology studies, clinical trials, and interdisciplinary research programs; and

"(2) establish programs of evaluation, planning, and dissemination of knowledge related to such research and training.

"INTERAGENCY COORDINATING COMMITTEES

"SEC. 429. (a) For the purpose of—

"(1) better coordination of the research activities of all the national research institutes relating to diabetes mellitus, digestive diseases, and kidney, urologic, and hematologic diseases; and

"(2) coordinating those aspects of all Federal health programs and activities relating to such diseases to assure the adequacy and technical soundness of such programs and activities and to provide for the full communication and exchange of information necessary to maintain adequate coordination of such programs and activities;

the Secretary shall establish a Diabetes Mellitus Interagency Coordinating Committee, a Digestive Diseases Interagency Coordinating Committee, and a Kidney, Urologic, and Hematologic Diseases Coordinating Committee (hereafter in this section individually referred to as a 'Committee').

"(b) Each Committee shall be composed of the Directors of each of the national research institutes and divisions involved in research with respect to the diseases for which the Committee is established, the Division Director of the Institute for the diseases for which the Committee is established, the Chief Medical Director of the Veterans' Administration, and the Assistant Secretary of Defense for Health Affairs (or the designees of such officers) and shall include representation from all other Federal departments and agencies whose programs involve health functions or responsibilities relevant to such diseases, as determined by the Secretary. Each Committee shall be chaired by the Director of NIH (or the designee of the Director). Each Committee shall meet at the call of the chairman, but not less often than four times a year.

"(c) Each Committee shall prepare an annual report for—

"(1) the Secretary;

"(2) the Director of NIH; and

"(3) the Advisory Board established under section 430 for the diseases for which the Committee was established,

detailing the work of the Committee in carrying out paragraphs (1) and (2) of subsection (a) in the fiscal year for which the report was prepared. Such report shall be submitted not later than 120 days after the end of each fiscal year.

"ADVISORY BOARDS

"SEC. 430. (a) The Secretary shall establish in the Institute the National Diabetes Advisory Board, the National Digestive Diseases Advisory Board, and the National Kidney and Urologic Diseases Advisory Board (hereafter in this section individually referred to as an 'Advisory Board').

"(b) Each Advisory Board shall be composed of eighteen appointed members and nonvoting ex officio members as follows:

"(1) The Secretary shall appoint—

"(A) twelve members from individuals who are scientists, physicians, and other health professionals, who are not officers or employees of the United States, and who represent the specialties and disciplines relevant to the diseases with respect to which the Advisory Board is established; and

"(B) six members from the general public who are knowledgeable with respect to such diseases, including at least one member who is a person who has such a disease and one member who is a parent of a person who has such a disease.

Of the appointed members at least five shall by virtue of training or experience be knowledgeable in the fields of health education, nursing, data systems, public information, and community program development.

"(2)(A) The following shall be ex officio members of each Advisory Board:

"(i) The Assistant Secretary for Health, the Director of NIH, the Director of the National Institute of Diabetes and Digestive and Kidney Diseases, the Director of the Centers for Disease Control, the Chief Medical Director of the Veterans' Administration, the Assistant Secretary of Defense for Health Affairs, and the Division Director of the National Institute of Diabetes and Digestive and Kidney Diseases for the diseases for which the Board is established (or the designees of such officers).

"(ii) Such other officers and employees of the United States as the Secretary determines necessary for the Advisory Board to carry out its functions.

"(B) In the case of the National Diabetes Advisory Board, the following shall also be ex officio members: The Director of the National Heart, Lung, and Blood Institute, the Director of the National Eye Institute, the Director of the National Institute of Child Health and Human Development, and the Administrator of the Health Resources and Services Administration (or the designees of such officers).

"(c) Members of an Advisory Board who are officers or employees of the Federal Government shall serve as members of the Advisory Board without compensation in addition to that received in their regular public employment. Other members of the Board shall receive compensation at rates not to exceed the daily equivalent of the annual rate in effect for grade GS-18 of the General Schedule for each day (including traveltime) they are engaged in the performance of their duties as members of the Board.

"(d) The term of office of an appointed member of an Advisory Board is four years, except that no term of office may extend beyond the expiration of the Advisory Board. Any member appointed to fill a vacancy for an unexpired term shall be appointed for the remainder of such term. A member may serve after the expiration of the member's term until a successor has taken office. If a vacancy occurs in an Advisory Board, the Secretary shall make an appointment to fill the vacancy not later than 90 days from the date the vacancy occurred.

"(e) The members of each Advisory Board shall select a chairman from among the appointed members.

"(f) The Secretary shall, after consultation with and consideration of the recommendations of an Advisory Board, provide the Advisory Board with an executive director and one other professional staff member. In addition, the Secretary shall, after consultation with and consideration of the recommendations of the Advisory Board, provide the Advisory Board with such additional professional staff members, such clerical staff members, such services of consultants, such information, and (through contracts or other arrangements) such administrative support services and facilities, as the Secretary determines are necessary for the Advisory Board to carry out its functions.

"(g) Each Advisory Board shall meet at the call of the chairman or upon request of the Director of the Institute, but not less often than four times a year.

"(h) The National Diabetes Advisory Board and the National Digestive Diseases Advisory Board shall—

"(1) review and evaluate the implementation of the plan (referred to in section 433) respecting the diseases with respect to which the Advisory Board was established and periodically update the plan to ensure its continuing relevance;

"(2) for the purpose of assuring the most effective use and organization of resources respecting such diseases, advise and make recommendations to the Congress, the Secretary, the Director of NIH, the Director of the Institute, and the heads of other appropriate Federal agencies for the implementation and revision of such plan; and

"(3) maintain liaison with other advisory bodies related to Federal agencies involved in the implementation of such plan, the coordinating committee for such diseases, and with key non-Federal entities involved in activities affecting the control of such diseases.

"(i) In carrying out its functions, each Advisory Board may establish subcommittees, convene workshops and conferences, and collect data. Such subcommittees may be composed of Advisory Board members and nonmember consultants with expertise in the particular area addressed by such subcommittees. The subcommittees may hold such meetings as are necessary to enable them to carry out their activities.

"(j) Each Advisory Board shall prepare an annual report for the Secretary which—

"(1) describes the Advisory Board's activities in the fiscal year for which the report is made;

"(2) describes and evaluates the progress made in such fiscal year in research, treatment, education, and training with respect to the diseases with respect to which the Advisory Board was established;

"(3) summarizes and analyzes expenditures made by the Federal Government for activities respecting such diseases in such fiscal year; and

"(4) contains the Advisory Board's recommendations (if any) for changes in the plan referred to in section 433.

"(k) Each Advisory Board shall expire on September 30, 1988.

"(l) The National Diabetes Advisory Board and the National Digestive Diseases Advisory Board in existence on the date of enactment of the Health Research Extension Act of 1985 shall terminate upon the appointment of a successor Board under subsection (a). The Secretary shall make appointments to the Advisory Boards established under subsection (a) before the expiration of 90 days after such date. The members of the Boards in existence on such date may be appointed, in accordance with subsections (b) and (d), to the Boards established under subsection (a) for diabetes and digestive diseases, except that at least one-half of the members of the National Diabetes Advisory Board in existence on the date of enactment of the Health Research Extension Act of 1985 shall be appointed to the National Diabetes Advisory Board first established under subsection (a).

"RESEARCH AND TRAINING CENTERS

"SEC. 431. (a)(1) Consistent with applicable recommendations of the National Commission on Diabetes, the Director of the Institute shall provide for the development or substantial expansion of centers for research and training in diabetes mellitus and related endocrine and metabolic diseases. Each center developed or expanded under this subsection shall—

"(A) utilize the facilities of a single institution, or be formed from a consortium of cooperating institutions, meeting such research and training qualifications as may be prescribed by the Secretary; and

"(B) conduct—

"(i) research in the diagnosis and treatment of diabetes mellitus and related endocrine and metabolic diseases and the complications resulting from such diseases;

"(iii) training programs for physicians and allied health personnel in current methods of diagnosis and treatment of such diseases and complications, and in research in diabetes; and

"(iii) information programs for physicians and allied health personnel who provide primary care for patients with such diseases or complications.

"(2) A center may use funds provided under paragraph (1) to provide stipends for nurses and allied health professionals enrolled in research training programs described in paragraph (1)(B)(ii).

"(b) Consistent with applicable recommendations of the National Digestive Diseases Advisory Board, the Director shall provide for the development or substantial expansion of centers for research in digestive diseases and related functional, congenital, metabolic disorders, and normal development of the digestive tract. Each center developed or expanded under this subsection—

"(1) shall utilize the facilities of a single institution, or be formed from a consortium of cooperating institutions, meeting such research qualifications as may be prescribed by the Secretary;

"(2) shall develop and conduct basic and clinical research into the cause, diagnosis, early detection, prevention, control, and treatment of digestive diseases and nutritional disorders and related functional, congenital, or metabolic complications resulting from such diseases or disorders;

"(3) shall encourage research into and programs for—

"(A) providing information for patients with such diseases and the families of such patients, physicians and others who care for such patients, and the general public;

"(B) model programs for cost effective and preventive patient care; and

"(C) training physicians and scientists in research on such diseases, disorders, and complications; and

"(4) may perform research and participate in epidemiological studies and data collection relevant to digestive diseases and disorders and disseminate such research, studies, and data to the health care profession and to the public.

"(c) The Director shall provide for the development or substantial expansion of centers for research in kidney and urologic diseases. Each center developed or expanded under this subsection—

"(1) shall utilize the facilities of a single institution, or be formed from a consortium of cooperating institutions, meeting such research qualifications as may be prescribed by the Secretary;

"(2) shall develop and conduct basic and clinical research into the cause, diagnosis, early detection, prevention, control, and treatment of kidney and urologic diseases;

"(3) shall encourage research into and programs for—

"(A) providing information for patients with such diseases, disorders, and complications and the families of such patients, physicians and others who care for such patients, and the general public;

"(B) model programs for cost effective and preventive patient care; and

"(C) training physicians and scientists in research on such diseases; and

"(4) may perform research and participate in epidemiological studies and data collection relevant to kidney and urologic diseases in order to disseminate such research, studies, and data to the health care profession and to the public.

"(d) Insofar as practicable, centers developed or expanded under this section should be geographically dispersed throughout the United States and in environments with proven research capabilities. Support of a center under this section may be for a period of not to exceed five years and such period may be extended by the Director of the Institute for additional periods of not more than five years each if the operations of such center have been reviewed by an appropriate technical and scientific peer review group established by the Director and if such group has recommended to the Director that such period should be extended.

"ADVISORY COUNCIL SUBCOMMITTEES

"SEC. 432. There are established within the advisory council for the Institute appointed under section 406 a subcommittee on diabetes and endocrine and metabolic diseases, a subcommittee on digestive diseases and nutrition, and a subcommittee on kidney, urologic, and hematologic diseases. The subcommittees shall be composed of members of the advisory council who are outstanding in the diagnosis, prevention, and treatment of the diseases for which the subcommittees are established and members of the advisory council who are leaders in the fields of education and public affairs. The subcommittees are authorized to review applications made to the Director of the Institute for grants for research and training projects relating to the diagnosis, prevention, and treatment of the diseases for which the subcommittees are established and shall recommend to the advisory council those applications and contracts that the subcommittees determine will best carry out the purposes of the Institute. The subcommittees shall also review and evaluate the diabetes and endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases programs of the Institute and recommend to the advisory council such changes in the administration of such programs as the subcommittees determine are necessary.

"BIENNIAL REPORT

"SEC. 433. The Director of the Institute shall prepare for inclusion in the biennial report made under section 407 a description of the Institute's activities—

"(1) under the current diabetes plan under the National Diabetes Mellitus Research and Education Act; and

"(2) under the current digestive diseases plan formulated under the Arthritis, Diabetes, and Digestive Diseases Amendments of 1976.

The description submitted by the Director shall include an evaluation of the activities of the centers supported under section 431.

FY 84 Funding

PROGRAM DESCRIPTION OF 12B

Benign Prostatic Hyperplasia(n=12): $2,042,404

Retinoids and Hormones
Antiandrogens-Biochemistry and Synthesis
Endocrinology/Cell Biology/Biochemistry(P01)
Cell Biology and Sex Steroid Binding
Developmental Biology
Endocrine Parameters-Testicular Irridation
Developmental Biology
Biochemistry of Prostate Secretions
Androgen Metabolism and Control
Growth Factors-Biochemistry, Immunology
Biochemistry-Phosphodiesterase
Growth Factors-Biochemistry, Immunology

Urolithiasis(n=13): $2,501,626 + $9,400

PtH and Vitamin D
Regulation and Synthesis of Vitamin D and Calcium Absorption
Kinetics of Growth and Dissolution of Minerals
Phosphate Reabsorption
Biochemistry/Physicochemistry/Physiology/Nutrition(P01)
Calcification and Vitamin D
Biochemistry/Physicochemistry/Biophysics(P01)
Metabolic Acidosis
Calcium Transport in Kidney Tubules
Biophysics of Crystal Growth
Physicochemistry and Immunochemistry of Stone Inhibitors
Pathogenesis of PtH and Stone Disease and Treatment(P01)
Internation Conference of Urolithiasis($9,400)

Urinary Tract Infection(n=4): $420,805

Immunization Against UTI
Host-Parasite Interaction in Pyelonephritis
Contraception and UTI
Adhesion and UTI(F06)

Urinary Tract(General; n=2): $113,613

Urology Training Grant(not paid in FY 84).
Histology and Function of Urothelium

Urinary Tract(Urodynamics/neurourology; n=4): $257,980

Contractile Mechanisms of Smooth Muscle
Purinergics in Urinary Tract
Autonomics and Lower Urinary Tract
Autonomic Control of Bladder and Lg Intestine

Urinary Tract(Surgery): $159,753

Congenital Hydronephrosis In-Utero

Urinary Tract(Reflux): $245,725

VUR Clinical Trials
Supplement for VUR Clinical Trials

Other Research(n=4): $381,008

Impotence in ERSD
Gordon Conference on Genital Tract
Cell Biology and Immunology-Peyronie's Disease
Genetics of Orotic Aciduria

TOTAL AWARDED IN PROGRAM 12B=$6,132,314

The following comments are submitted by the National Kidney Foundation in conjunction with the administrative review of the disease research programs of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) as required by Public Law 99-158.

1. The current administrative structure of NIDDK is appropriate and the disease research programs remaining after the creation of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) are compatible. The growth, development and scientific productivity of these programs would not be enhanced if administered or conducted by other components of NIH. In fact, the various disciplines are interracting well in the intramural program which is providing an integrative focus, as the director of the program has shown.

2. Our main concern is in the area of staffing. In relation to other Institutes, staffing at NIDDK is lowest both in number of positions and in funds devoted to staff. Increasing funding for staff will expand the effectiveness of NIDDK's scientific program. This is especially true for the intramural program which shows great potential. Conversely, we want to be sure that NIAMS is not staffed by transferring positions from NIDDK, which is already under-staffed.

We appreciate the opportunity to participate in the briefing on July 1 and will expand upon our position at that time.

Robert W. Schrier, M.D.
President
National Kidney Foundation, Inc.

HEALTH AND MEDICINE COUNSEL OF WASHINGTON

400 FIRST STREET, N.W., SUITE 712 WASHINGTON, D.C. 20001 (202) 347-7878

HARLEY M. DIRKS President
DALE P. DIRKS Vice President for Governmental Relations

Summary of Presentation

by

Harley M. Dirks
President
Health and Medicine Counsel of Washington

Legislative Consultant
American College of Gastroenterology

and

Digestive Disease National Coalition

before

The Committee
review
disease research programs

of

The National Institute of Diabetes
and Digestive and Kidney Diseases

The Digestive Disease National Coalition and the American College of Gastroenterology believe that the current overall structure of the National Institute of Diabetes and Digestive and Kidney Diseases is both efficient and effective. We applaud the Institute's fine work, innovative efforts, and coordinated approach to solving the problems associated with digestive diseases.

We would, however, like to offer a few suggestions for improving current programs within the Institute. One suggestion concerns the need for better utilization of the Administrative costs allocated for the operations of the Institute. We believe that strengthening the evaluation procedures for determining the Federal resources required for Administrative and operating costs would result in greater funding allocations for digestive disease research grants.

A second recommendation concerns establishing mechanisms for better integration of efforts among the Institute's programs. To an extend, this is now being done, but we would like to emphasize the need for constant and continual sharing of the latest data and information available.

Finally, we would suggest that representation on the Institute's Advisory Council reflect a balancing of basic and clinical researchers. We believe that representation from both areas of expertise is vitally important to successful program implementation and evaluation.

Once again, the present structure of the NIDDK has been highly successful, and we commend the Administrators of this most vital research institute. The suggestions we have outlined are for further improving the excellent work currently being done.

ONE PAGE SUMMARY: STATEMENT OF
JEAN G. BACON, EXECUTIVE DIRECTOR
POLYCYSTIC KIDNEY RESEARCH FOUNDATION
KANSAS CITY, MISSOURI 64105
before
SPECIAL NIH COMMITTEE
TUESDAY, JULY 1, 1986 1:00 P.M.

Thank you for the opportunity to speak to you about the recent reorganization of NIDDK. The Polycystic Kidney Research Foundation accepts this reorganization and feels that the reassignment of the arthritis disease group will free NIDDK to concentrate more heavily on the growing importance of kidney disorders, and more specifically polycystic kidney disease. Autosomal dominant polycystic kidney disease (ADPKD) afflicts one in every 500 to 1,000 persons in the United States, a total number equal to the population of Kansas City, Missouri, slightly less than 500,000. In as much as NIDDK does provide the major federal support for research of polycystic kidney disease, we welcome this important elevation of our interests. We think that research of polycystic kidney disorders is on the brink of important breakthroughs. At a time when many genetic diseases have risen to the forefront of medical research, both adult and infantile polycystic kidney diseases have joined Huntington's disease, cystic fibrosis and muscular dystrophy in attracting attention.

The revivial of interest in polycystic kidney disease among the Nephrology research community comes at the opportune time when great advances have been made in fundamental research in genetics and molecular biology. The recent discovery that the gene defect for autosomal dominant polycystic kidney disease is located on the short arm of chromosome 16, represents a giant step towards isolating the defective DNA and determining the abnormal gene products.

Although the Polycystic Kidney Research Foundation's scientific community does not support further fragmentation of NIH, we do support the present reorganization and administrative framework as the best vehicle for meeting our specific needs.

STATEMENT OF
Ms. Jean G. Bacon, Executive Director
POLYCYSTIC KIDNEY RESEARCH FOUNDATION
Kansas City, Missouri 64105
Before
SPECIAL NIH COMMITTEE
Tuesday, July 1, 1986, 1:00 P.M.

Thank you for the opportunity to speak to you this afternoon about the recent reorganization of NIDDK. My comments reflect the position of the Polycystic Kidney Research Foundation headquartered in Kansas City, Missouri.

The Foundation was founded in 1982 by Joseph H. Bruening, a retired Kansas City realtor. The goal of the Foundation is to promote both public awareness of the disease and research into the cause and cure of the illness. The Foundation maintains an international list of 1,700 patients, families, friends, and health professionals. Recently we have begun to support small specialized research grant projects approved by the Foundation's Scientific Advisors who collectively represent the most advanced national research technologies dedicated to the cause and cure of polycystic kidney disease. Their names and institutions appear on the attached letterhead. A genetic roster is being developed jointly by the Foundation and Indiana University School of Medicine to identify inherited disease traits to assist research.

The Foundation sponsored the First International Workshop on Problems in Diagnosis and Management of Polycystic Kidney Disease in September of 1984. Twenty-five medical researchers from the United States and Europe gathered in Kansas City to report on recent developments in the treatment of the disease. A book has been published documenting the proceedings of this workshop, the first ever convened.

Over the last three years, the Foundation and NIDDK have collaborated on a three year research program project grant involving the University of New Mexico, University of Kansas, Indiana University and Northwestern University. Apart from the federal resources committed to this project, the Foundation is funding a multi-year companion study at the Oregon Health Sciences University. In 1985, NIDDK funded a second multi-year study through the University of Colorado Health Sciences Center.

Given the close relationship between the Foundation and NIDDK, the Foundation can positively support the reorganization. The reassignment of the arthritis disease group frees NIDDK to concentrate more heavily on the growing importance of kidney disorders, more specifically polycystic kidney disease.

Autosomal dominant polycystic kidney disease (APKD) afflicts one in every 500 to 1,000 persons in the United States. If all the pkd victims in the U.S. were put in one place, they would equal the population of Kansas City, Missouri, slightly less than 500,000. As you know, NIDDK provides the major federal support for research of polycystic kidney disease. We are pleased to have our interests elevated to a more important position within NIDDK.

The Foundation believes that the research of polycystic kidney disease is on the brink of important breakthroughs. As you know, genetic diseases have risen to the forefront of medical research. Both adult and infantile polycystic kidney diseases have joined Huntington's disease, cystic fibrosis and muscular dystrophy in attracting major attention.

The nephrology research community has revived its interest in polycystic kidney disease at an opportune time. Great advances continue to be currently made in fundamental research in genetics and molecular biology. These advances have led to an important recent discovery. The gene defect for autosomal dominant polycystic kidney disease has been located on the short arm of chromosone 16. This discovery is a giant step toward isolating the defective DNA and thereby determining the abnormal gene products.

It should be stated that the Foundation's scientific community does not support further fragmentation of NIH. However, we do enthusiastically support the present reorganization and administrative framework. For us, this is the best vehicle to meet our specific needs.

Thank you.

STATEMENT OF THE

AMERICAN SOCIETY OF HEMATOLOGY

TO THE

NIDDK ADMINISTRATIVE REVIEW COMMITTEE

JULY 1, 1986

PRESENTED BY

RICHARD COOPER, M.D.
DEAN, MEDICAL COLLEGE OF WISCONSIN
CHAIRMAN, PUBLIC EDUCATION COMMITTEE
AMERICAN SOCIETY OF HEMATOLOGY

Blood is a diverse mixture of cellular and fluid constituents with a vast range of normal functional qualities. These qualities impact on every organ system of the human body. For example, all tissues depend on red blood cells for the delivery of oxygen. Granulocytes influence the body's defenses against infection. Lymphocytes impact upon the immune response and on diseases such as AIDS. Platelets and coagulant proteins impact on the control of hemostasis and on occlusive vascular diseases, such as strokes and myocardial infarction. Malignant disorders affecting the cellular constituents of blood lead to diseases such as the leukemias and the lymphomas.

Basic studies of normal blood cells have taught us a great deal about hematologic diseases. These studies also have provided information applicable to cells from other, less-readily sampled tissues. Examples include our knowledge of membrane structure, ion permeability, surface antigen distribution, transplantation, protein synthesis, and molecular biology. Thus, hematologic research has had an impact on research progress in many organ systems.

Because of the diverse influences of blood on many organ systems, and because of the applicability of hematologic research to questions pertaining to these organ systems, several NIH institutes have found it important to support various aspects of blood research. NIDDK has had long-standing interests in studies of the basic metabolism, physiology and chemistry of normal blood cells. These interests have led to the present hematology program within NIDDK, which concentrates heavily on studies of the structure and permeability of blood cell membranes, studies of the synthesis and structure of both heme and globin, and studies of normal hematopoiesis and of bone marrow transplantation. Many of these studies overlap with other programmatic interests within NIDDK. For example, studies of glycosylated hemoglobin are important in diabetes research. Similarly, studies of the cellular constituents of the kidney are important in our understanding of the synthesis of erythropoietin, a hormone produced in the kidney which stimulates erythropoiesis. Renal transplantation, as well as the transplantation of other organs, depends on immunologic studies of leukocytes antigens.

The Hematology Research Program of NIDDK interfaces with research conducted under the auspices of NCI, which deals with both normal and malignant hematopoiesis and lymphopoiesis. An interface also exists with hematology research supported by NIAID, which deals with the immune response and the defense against infection. A large and important interface exists with NHLBI.

Only NIDDK and NHLBI have specific authorizations designated for hematologic research. NHLBI has assumed the major responsibility for studies of coagulant proteins and platelets, so important in normal hemostasis and in vascular occlusion; studies of normal oxygen delivery to tissues and of red cell abnormalities, such as Sickle Cell Disease, in which local delivery of oxygen is so radically disturbed; and studies of the transfusion of blood components. NHLBI and NIDDK interface in areas of common interest, such as hematopoiesis, transplantation and molecular biology. The smaller NIDDK Hematology Program budget is directed almost exclusively toward basic research. The larger NHLBI budget is also able to support clinical trials, specialized centers and program projects.

The complementary nature of hematology research support mechanisms in NIDDK, NHLBI, NCI, and, to a lesser extent, other institutes, has been acknowledged and advocated in Congressional legislation. This includes the Senate Appropriations Bill Report for FY 86, appropriation bills for FY 83, 84 and 85, and the NIH Reauthorization Bill of October, 1985. This latter bill specifically mandated NIDDK support of hematologic research. In addition, it called for an Interagency Coordinating Committee for kidney, urology and hematologic diseases to bridge institutes.

I have tried to indicate that hematologic research is intrinsically diverse. It is supported by a diversity of institutes which consider it to be an essential part of their research mandate. In turn, hematologic research has added strength to programs throughout these institutes. The Hematology Program of NIDDK is an important element in the spectrum of diversity. There is strength in the diversity of hematologic research supported by the NIH, and there is strength in the diversity of institutes which embrace that research. I hope this diversity will be permitted to continue.

99TH CONGRESS 1st Session | HOUSE OF REPRESENTATIVES | REPORT 99-289

DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATION BILL, 1986

SEPTEMBER 26, 1985.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

Mr. NATCHER, from the Committee on Appropriations, submitted the following

REPORT

system and the kidney, nutrition and the kidney, immunology and the kidney, and cellular injury and the kidney.

The Committee received the Report on Establishment of the Urology Research Coordinating Committee and on Federal Urology Research Efforts. A number of Federal agencies and urology community representatives were involved in preparing this report. The Institute sponsored a conference on benign prostatic hyperplasia—a condition that affects nearly 80 percent of men over the age of 60 and that often requires surgery. The Committee encourages the Institute to address the need for developing appropriate animal models of this disease, and to direct additional research efforts to preventing it.

Hematology research is pursued by several NIH institutes. The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases supports research including projects on normal blood cell formation, basic research with relevance to blood disorders such as Cooley's anemia, and histocompatibility matching in support of transplantation activities. Grantees have cloned the gene for human erythropoietin—a hormone that stimulates red blood cell production. Synthetic erythropoietin has potential for research purposes and for diagnosis and treatment of a variety of anemias.

The Committee has deferred considerations of appropriations for research training which are not authorized for fiscal year 1986. The 1985 appropriations for these programs amounted to $26,730,000. The increased funds provided in the bill will fund the full amounts currently estimated to be required for non-competing continuations of research project grants, and will provide an estimated $111,013,000 for competing continuations and new grants, an increase of $3,560,000 over the 1985 dollar level. The total amount available for regular research grants will rise by $28,870,000.

98TH CONGRESS
2d Session
HOUSE OF REPRESENTATIVES
REPORT
98-911

DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATION BILL, 1985

JULY 26, 1984.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

Mr. NATCHER, from the Committee on Appropriations, submitted the following

REPORT

[To accompany H.R 6028]

task of compiling all Federal urology research efforts in all agencies, including specific grants and funding amounts, such compilation to be completed prior to the fiscal year 1986 appropriations hearings.

New knowledge is accumulating in the area of blood diseases. Scientists have purified a human blood factor essential to stimulating and controlling the production of blood cells in bone marrow. A new, sensitive and less risky assay has been developed for prenatal diagnosis of sickle-cell anemia. An experimental method for delivering medication to animals with Cooley's anemia holds promise as a possible means of controlling iron overload in humans with this disease. In various anemias, new knowledge about genetic defects and abnormalities in gene expression are paving the way for the development of drug therapies, such as the use of the cancer drug, 5-azacytidine, to treat Cooley's anemia and sickle-cell disease. The Committee is aware of the efforts of both the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases and the National Heart, Lung and Blood Institute in blood diseases research and supports the current coordinated approach to this field at the NIH.

This Institute supports research on a great variety of diseases. The Committee is aware of the Institute's efforts to effect a resource allocation process in which scientific excellence, public health needs, and many other factors are considered. Important aspects of this process are continuous dialogue with the scientific and lay communities and adjustments in resource allocations throughout the year, in response to emerging scientific needs and opportunities. The Institute is urged to continue to review and refine this process.

98TH CONGRESS | HOUSE OF REPRESENTATIVES | REPORT
1st Session | No. 98-357

DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATION BILL, 1984

SEPTEMBER 16, 1983.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

Mr. NATCHER, from the Committee on Appropriations, submitted the following

REPORT

together with

SUPPLEMENTAL VIEWS

[To accompany H.R. 3913]

stone-formers. Regarding end-stage renal disease, the Committee heard testimony describing the Institute's efforts to respond to Congressional directives for a study of nutritional therapy in this area. Institute-supported research on nutrition and kidney disease has increased considerably in recent years, and the Committee believes the Institute is taking reasonable and responsible steps to plan for a research initiative on the effects of nutritional therapy on the rate of progression of renal disease. Other research in the field of urology is designed to develop a greater understanding of the causes of benign prostatic hyperplasia (enlargement of the prostrate) and to study loss of kidney function secondary to back-up urine from the bladder. The Committee encourages the training of researchers in the field of urology, to create a nucleus of future leaders in this field.

Hematology and nutrition are two critical NIADDK program areas that contribute to research on many categorical diseases within the Institute's mission. Recent hematology advances hold the hope of chemically modifying defective genes or blood proteins to correct diseases of abnormal hemoglobin such as sickle-cell anemia and thalassemia. In addition to its importance in kidney disease, nutrition research is highly relevant to diabetes. In non-insulin dependent diabetes, it is now recognized that most patients are obese and that caloric restriction designed to reduce body weight to normal is the cornerstone of therapy. The Committee is aware that the hematology and nutrition programs of NIADDK are well-coordinated with related programs in other Institutes, and endorses this broad approach to these two fields.

99TH CONGRESS } SENATE { REPORT
1st Session } { 99-000

DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION AND RELATED AGENCIES APPROPRIATION BILL, 1986

Mr. WEICKER, from the Committee on Appropriations, submitted the following

REPORT

[To accompany H.R. 3424]

search has shown that the formation and recurrence of some types of kidney stones can be inhibited or prevented by drugs recently approved by the Food and Drug Administration. The Committee is pleased to receive the report it had requested detailing Federal efforts in urology research.

The Committee believes that the science in kidney/urology diseases has advanced to levels that suggest the Institute should give consideration to establishing centers of excellence in kidney disease, that emphasizes its relationship to nutrition, hypertension, diabetes mellitus, immunology, and obstructive and heredity diseases of the urological system.

Hematology research

The Committee endorses the active NIADDK support of hematology research. This productive research area cuts across several institutes and disciplines and the Committee believes this diversified but coordinated approach has been effective and should continue. Substantial progress has been made in blood diseases research, particularly related to erythropoietin, a hormone that stimulates red blood cell production in bone marrow. The gene for erythropoietin has been cloned and is now being used to synthesize this hormone in tissue culture. Other advances in hematology include construction of molecular maps of several important human genes, including the ones for hemoglobin, and treatment of diseases such as aplastic anemia and inborn errors of metabolism by transplanting healthy bone marrow tissue.

NIADDK basic and clinical researchers are making substantial progress in understanding the causes of chronic diseases within the Institute's mission, and the Committee anticipates further development of effective therapies and preventive approaches to these diseases.

On October 7, 1985:

H.R. 1042. An act to grant a Federal charter to the Pearl Harbor Survivors Association.

On October 8, 1985:

H.J. Res. 393. Joint resolution to provide for the temporary extension of certain programs relating to housing and community development, and for other purposes.

CONFERENCE REPORT ON H.R. 2409

Mr. DINGELL submitted the following conference report and statement on the bill (H.R. 2409) to amend the Public Health Service Act to revise and extend the authorities under that Act relating to the National Institutes of Health and National Research Institutes, and for other purposes:

CONFERENCE REPORT (H.R. REPT. 99-309)

The committee of conference on the disagreeing votes of the two Houses on the amendment of the Senate to the bill (H.R. 2409) to amend the Public Health Service Act to revise and extend the authorities under that Act relating to the National Institutes of Health and National Research Institutes, and for other purposes, having met, after full and free conference, have agreed to recommend and do recommend to their respective Houses as follows:

That the House recede from its disagreement to the amendment of the Senate and agree to the same with an amendment as follows:

In lieu of the matter proposed to be inserted by the Senate amendment insert the following:

SECTION 1. SHORT TITLE; REFERENCE TO ACT; AND TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Health Research Extension Act of 1985".

(b) REFERENCE TO ACT.—Except as otherwise specifically provided, whenever in this Act an amendment or repeal is expressed in terms of an amendment to, or repeal of, a section or other provision, the reference shall be considered to be a reference to a section or other provision of the Public Health Service Act.

(c) TABLE OF CONTENTS.—

"Subpart 3—National Institute of Diabetes and Digestive and Kidney Diseases

"PURPOSE OF THE INSTITUTE

"SEC. 426. The general purpose of the National Institute of Diabetes and Digestive and Kidney Diseases (hereafter in this subpart referred to as the 'Institute') is the conduct and support of research, training, health information dissemination, and other programs with respect to diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and kidney, urologic, and hematologic diseases.

"DATA SYSTEMS AND INFORMATION CLEARINGHOUSES

"SEC. 427. (a) The Director of the Institute shall (1) establish the National Diabetes Data System for the collection, storage, analysis, retrieval, and dissemination of data derived from patient populations with diabetes, including, where possible, data involving general populations for the purpose of detection of individuals with a risk of developing diabetes, and (2) establish the National Diabetes Information Clearinghouse to facilitate and enhance knowledge and understanding of diabetes on the part of health professionals, patients, and the public through the effective dissemination of information.

"(b) The Director of the Institute shall (1) establish the National Digestive Diseases Data System for the collection, storage, analysis, retrieval, and dissemination of data derived from patient populations with digestive diseases, including, where possible, data involving general populations for the purpose of detection of individuals with a risk of developing digestive diseases, and (2) establish the National Digestive Diseases Information Clearinghouse to facilitate and enhance knowledge and understanding of digestive diseases on the part of health professionals, patients, and the public through the effective dissemination of information.

"(c) The Director of the Institute shall (1) establish the National Kidney and Urologic Diseases Data System for the collection, storage, analysis, retrieval, and dissemination of data derived from patient populations with kidney and urologic diseases, including, where possible, data involving general populations for the purpose of detection of individuals with a risk of developing kidney and urologic diseases and (2) establish the National Kidney and Urologic Diseases Information Clearinghouse to facilitate and enhance knowledge and understanding of kidney and urologic diseases on the part of health professionals, patients, and the public through the effective dissemination of information.

"DIVISION DIRECTORS FOR DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES, DIGESTIVE DISEASES AND NUTRITION, AND KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES

"SEC. 428. (a)(1) In the Institute there shall be a Division Director for Diabetes, Endocrinology, and Metabolic Diseases, a Division Director for Digestive Diseases and Nutrition, and a Division Director for Kidney, Urologic, and Hematologic Diseases. Such Division Directors, under the supervision of the Director of the Institute, shall be responsible for—

"(A) developing a coordinated plan (including recommendations for expenditures) for each of the national research institutes within the National Institutes of Health with respect to research and training concerning diabetes, endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases;

"(B) assessing the adequacy of management approaches for the activities within such institutes concerning such diseases and nutrition and developing improved approaches if needed;

"(C) monitoring and reviewing expenditures by such institutes concerning such diseases and nutrition; and

"(D) identifying research opportunities concerning such diseases and nutrition and recommending ways to utilize such opportunities.

"(2) The Director of the Institute shall transmit to the Director of NIH the plans, recommendations, and reviews of the Division Directors under subparagraphs (A) through (D) of paragraph (1) together with such comments and recommendations as the Director of the Institute determines appropriate.

"(b) The Director of the Institute, acting through the the Division Director for Diabetes, Endocrinology, and Metabolic Diseases, the Division Director for Digestive Diseases and Nutrition, and the Division Director for Kidney, Urologic, and Hematologic Diseases, shall—

"(1) carry out programs of support for research and training (other than training for which National Research Service Awards may be made under section 487) in the diagnosis, prevention, and treatment of diabetes mellitus and endocrine and metabolic diseases, digestive diseases and nutritional disorders, and kidney, urologic, and hematolog-

tic diseases, including support for training in medical schools, graduate clinical training, graduate training in epidemiology, epidemiology studies, clinical trials, and interdisciplinary research programs; and

"(2) establish programs of evaluation, planning, and dissemination of knowledge related to such research and training.

"INTERAGENCY COORDINATING COMMITTEES

"SEC. 429. (a) For the purpose of—

"(1) better coordination of the research activities of all the national research institutes relating to diabetes mellitus, digestive diseases, and kidney, urologic, and hematologic diseases; and

"(2) coordinating those aspects of all Federal health programs and activities relating to such diseases to assure the adequacy and technical soundness of such programs and activities and to provide for the full communication and exchange of information necessary to maintain adequate coordination of such programs and activities;

the Secretary shall establish a Diabetes Mellitus Interagency Coordinating Committee, a Digestive Diseases Interagency Coordinating Committee, and a Kidney, Urologic, and Hematologic Diseases Coordinating Committee (hereafter in this section individually referred to as a 'Committee').

"(b) Each Committee shall be composed of the Directors of each of the national research institutes and divisions involved in research with respect to the diseases for which the Committee is established, the Division Director of the Institute for the diseases for which the Committee is established, the Chief Medical Director of the Veterans' Administration, and the Assistant Secretary of Defense for Health Affairs (or the designees of such officers) and shall include representation from all other Federal departments and agencies whose programs involve health functions or responsibilities relevant to such diseases, as determined by the Secretary. Each Committee shall be chaired by the Director of NIH (or the designee of the Director). Each Committee shall meet at the call of the chairman, but not less often than four times a year.

"(c) Each Committee shall prepare an annual report for—

"(1) the Secretary;

"(2) the Director of NIH; and

"(3) the Advisory Board established under section 430 for the diseases for which the Committee was established,

detailing the work of the Committee in carrying out paragraphs (1) and (2) of subsection (a) in the fiscal year for which the report was prepared. Such report shall be submitted not later than 120 days after the end of each fiscal year.

"ADVISORY BOARDS

"SEC. 430. (a) The Secretary shall establish in the Institute the National Diabetes Advisory Board, the National Digestive Diseases Advisory Board, and the National Kidney and Urologic Diseases Advisory Board (hereafter in this section individually referred to as an 'Advisory Board').

"(b) Each Advisory Board shall be composed of eighteen appointed members and nonvoting ex officio members as follows:

"(1) The Secretary shall appoint—

"(A) twelve members from individuals who are scientists, physicians, and other health professionals, who are not officers or employees of the United States, and who represent the specialties and disciplines relevant to the diseases with respect to which the Advisory Board is established; and

"(B) six members from the general public who are knowledgeable with respect to such diseases, including at least one member who is a person who has such a disease and one member who is a parent of a person who has such a disease.

Of the appointed members at least five shall by virtue of training or experience be knowledgeable in the fields of health education, nursing, data systems, public information, and community program development.

"(2)(A) The following shall be ex officio members of each Advisory Board:

"(i) The Assistant Secretary for Health, the Director of NIH, the Director of the National Institute of Diabetes and Digestive and Kidney Diseases, the Director of the Centers for Disease Control, the Chief Medical Director of the Veterans' Administration, the Assistant Secretary of Defense for Health Affairs, and the Division Director of the National Institute of Diabetes and Digestive and Kidney Diseases for the diseases for which the Board is established (or the designees of such officers).

"(ii) Such other officers and employees of the United States as the Secretary determines necessary for the Advisory Board to carry out its functions.

"(B) In the case of the National Diabetes Advisory Board, the following shall also be ex officio members: The Director of the National Heart, Lung, and Blood Institute, the Director of the National Eye Institute, the Director of the National Institute of Child Health and Human Development, and the Administrator of the Health Resources and Services Administration (or the designees of such officers).

"(c) Members of an Advisory Board who are officers or employees of the Federal Government shall serve as members of the Advisory Board without compensation in addition to that received in their regular public employment. Other members of the Board shall receive compensation at rates not to exceed the daily equivalent of the annual rate in effect for grade GS-18 of the General Schedule for each day (including traveltime) they are engaged in the performance of their duties as members of the Board.

"(d) The term of office of an appointed member of an Advisory Board is four years, except that no term of office may extend beyond the expiration of the Advisory Board. Any member appointed to fill a vacancy for an unexpired term shall be appointed for the remainder of such term. A member may serve after the expiration of the member's term until a successor has taken office. If a vacancy occurs in an Advisory Board, the Secretary shall make an appointment to fill the vacancy not later than 90 days from the date the vacancy occurred.

"(e) The members of each Advisory Board shall select a chairman from among the appointed members.

"(f) The Secretary shall, after consultation with and consideration of the recommendations of an Advisory Board, provide the Advisory Board with an executive director and one other professional staff member. In addition, the Secretary shall, after consultation with and consideration of the recommendations of the Advisory Board, provide the Advisory Board with such additional professional staff members, such clerical staff members, such services of consultants, such information, and (through contracts or other arrangements) such administrative support services and facilities, as the Secretary determines are necessary for the Advisory Board to carry out its functions.

"(g) Each Advisory Board shall meet at the call of the chairman or upon request of the Director of the Institute, but not less often than four times a year.

"(h) The National Diabetes Advisory Board and the National Digestive Diseases Advisory Board shall—

"(1) review and evaluate the implementation of the plan (referred to in section 433) respecting the diseases with respect to which the Advisory Board was established and periodically update the plan to ensure its continuing relevance;

"(2) for the purpose of assuring the most effective use and organization of resources respecting such diseases, advise and make recommendations to the Congress, the Secretary, the Director of NIH, the Director of the Institute, and the heads of other appropriate Federal agencies for the implementation and revision of such plan; and

"(3) maintain liaison with other advisory bodies related to Federal agencies involved in the implementation of such plan, the coordinating committee for such diseases, and with key non-Federal entities involved in activities affecting the control of such diseases.

"(i) In carrying out its functions, each Advisory Board may establish subcommittees, convene workshops and conferences, and collect data. Such subcommittees may be composed of Advisory Board members and nonmember consultants with expertise in the particular area addressed by such subcommittees. The subcommittees may hold such meetings as are necessary to enable them to carry out their activities.

"(j) Each Advisory Board shall prepare an annual report for the Secretary which—

"(1) describes the Advisory Board's activities in the fiscal year for which the report is made;

"(2) describes and evaluates the progress made in such fiscal year in research, treatment, education, and training with respect to the diseases with respect to which the Advisory Board was established;

"(3) summarizes and analyzes expenditures made by the Federal Government for activities respecting such diseases in such fiscal year; and

"(4) contains the Advisory Board's recommendations (if any) for changes in the plan referred to in section 433.

"(k) Each Advisory Board shall expire on September 30, 1988.

"(l) The National Diabetes Advisory Board and the National Digestive Diseases Advisory Board in existence on the date of enactment of the Health Research Extension Act of 1985 shall terminate upon the appointment of a successor Board under subsection (a). The Secretary shall make appointments to the Advisory Boards established under subsection (a) before the expiration of 90 days after such date. The members of the Boards in existence on such date may be appointed, in accordance with subsections (b) and (d), to the Boards established under subsection (a) for diabetes and digestive diseases, except that at least one-half of the members of the National Diabetes Advisory Board in existence on the date of enactment of the Health Research Extension Act of 1985 shall be appointed to the National Diabetes Advisory Board first established under subsection (a).'

"RESEARCH AND TRAINING CENTERS

"SEC. 431. (a)(1) Consistent with applicable recommendations of the National Commission on Diabetes, the Director of the Institute shall provide for the development or substantial expansion of centers for research and training in diabetes mellitus and related endocrine and metabolic diseases. Each center developed or expanded under this subsection shall—

"(A) utilize the facilities of a single institution, or be formed from a consortium of cooperating institutions, meeting such research and training qualifications as may be prescribed by the Secretary; and

"(B) conduct—

"(i) research in the diagnosis and treatment of diabetes mellitus and related endocrine and metabolic diseases and the complications resulting from such diseases;

"(ii) training programs for physicians and allied health personnel in current methods of diagnosis and treatment of such diseases and complications, and in research in diabetes; and

"(iii) information programs for physicians and allied health personnel who provide primary care for patients with such diseases or complications.

"(2) A center may use funds provided under paragraph (1) to provide stipends for nurses and allied health professionals enrolled in research training programs described in paragraph (1)(B)(ii).

"(b) Consistent with applicable recommendations of the National Digestive Diseases Advisory Board, the Director shall provide for the development or substantial expansion of centers for research in digestive diseases and related functional, congenital, metabolic disorders, and normal development of the digestive tract. Each center developed or expanded under this subsection—

"(1) shall utilize the facilities of a single institution, or be formed from a consortium of cooperating institutions, meeting such research qualifications as may be prescribed by the Secretary;

"(2) shall develop and conduct basic and clinical research into the cause, diagnosis, early detection, prevention, control, and treatment of digestive diseases and nutritional disorders and related functional, congenital, or metabolic complications resulting from such diseases or disorders;

"(3) shall encourage research into and programs for—

"(A) providing information for patients with such diseases and the families of such patients, physicians and others who care for such patients, and the general public;

"(B) model programs for cost effective and preventive patient care; and

"(C) training physicians and scientists in research on such diseases, disorders, and complications; and

"(4) may perform research and participate in epidemiological studies and data collection relevant to digestive diseases and disorders and disseminate such research, studies, and data to the health care profession and to the public.

"(c) The Director shall provide for the development or substantial expansion of centers for research in kidney and urologic diseases. Each center developed or expanded under this subsection—

"(1) shall utilize the facilities of a single institution, or be formed from a consortium of cooperating institutions, meeting such research qualifications as may be prescribed by the Secretary;

"(2) shall develop and conduct basic and clinical research into the cause, diagnosis, early detection, prevention, control, and treatment of kidney and urologic diseases;

"(3) shall encourage research into and programs for—

"(A) providing information for patients with such diseases, disorders, and complications and the families of such patients, physicians and others who care for such patients, and the general public;

"(B) model programs for cost effective and preventive patient care; and

"(C) training physicians and scientists in research on such diseases; and

"(4) may perform research and participate in epidemiological studies and data collection relevant to kidney and urologic diseases in order to disseminate such research, studies, and data to the health care profession and to the public.

"(d) Insofar as practicable, centers developed or expanded under this section should be geographically dispersed throughout the United States and in environments with proven research capabilities. Support of a center under this section may be for a period of not to exceed five years and such period may be extended by the Director of the Institute for additional periods of not more than five years each if the operations of such center have been reviewed by an appropriate technical and scientific peer review group established by the Director and if such group has recommended to the Director that such period should be extended.

"ADVISORY COUNCIL SUBCOMMITTEES

"SEC. 432. There are established within the advisory council for the Institute appointed under section 406 a subcommittee on diabetes and endocrine and metabolic diseases, a subcommittee on digestive diseases and nutrition, and a subcommittee on kidney, urologic, and hematologic diseases. The subcommittees shall be composed of members of the advisory council who are outstanding in the diagnosis, prevention, and treatment of the diseases for which the subcommittees are established and members of the advisory council who are leaders in the fields of education and public affairs. The subcommittees are authorized to review applications made to the Director of the Institute for grants for research and training projects relating to the diagnosis, prevention, and treatment of the diseases for which the subcommittees are established and shall recommend to the advisory council those applications and contracts that the subcommittees determine will best carry out the purposes of the Institute. The subcommittees shall also review and evaluate the diabetes and endocrine and metabolic diseases, digestive diseases and nutrition, and kidney, urologic, and hematologic diseases programs of the Institute and recommend to the advisory council such changes in the administration of such programs as the subcommittees determine are necessary.

"BIENNIAL REPORT

"SEC. 433. The Director of the Institute shall prepare for inclusion in the biennial report made under section 407 a description of the Institute's activities—

"(1) under the current diabetes plan under the National Diabetes Mellitus Research and Education Act; and

"(2) under the current digestive diseases plan formulated under the Arthritis, Diabetes, and Digestive Diseases Amendments of 1976.

The description submitted by the Director shall include an evaluation of the activities of the centers supported under section 431.

National Foundation for
Ileitis & Colitis

National Headquarters 444 Park Avenue South, New York, N.Y. 10016 • (212) 685-3440

Non-profit...research oriented.

June 18, 1986

Thomas E. Malone, Ph.D.
Chairman,
Comm. for Administrative Review
of the Programs of NIDDK
% Mr. Edward Lynch
National Institutes of Health
Building 1, Room 228
9000 Rockville Pike
Bethesda, MD. 20892

Dear Dr. Malone:

Thank you for the opportunity on July 1st to express the concerns I share with 25,000 members of the National Foundation for Ileitis and Colitis regarding the review of the Digestive Disease Research Program at the NIDDK.

NFIC itself is engaged in basic and clinical research concerning two serious intestinal diseases - Crohn's Disease and ulcerative colitis which affect upwards of 2 million Americans. Our Research Program has alerted us to the vicissitudes of scientific research and enables me to respond with some certainty to the questions being raised in this current review of the NIDDK.

This year NFIC is funding $1.3 million in investigator-initiated Research Grants, Research Fellowships and Career Development Awards. We are proud of our research program which, from its inception over 18 years ago, has carefully emulated the best of the NIH Research Program and its Peer Review System.

NFIC and the DD Division of the NIH have often performed as partners in IBD research since the Division's inclusion as a high priority and visible focus within the NIADDK in the early 1970's.

(over)

We have co-sponsored major scientific conferences and have trained and supported young investigators who have then later been awarded significant NIH grants in promising areas of research. We call such impact "NFIC's Multiplier Effect" and we are pleased to report that of the last 25 IBD-related NIH supported projects, 20 of the investigators were originally funded by NFIC.

NFIC's Research Program, similiar to NIH's DD Program, has achieved and maintained a consistent level of excellence even in the light of budgetary constraints and the quickly shifting dynamics required of any good nationally coordinated scientific program on the "cutting edge."

The NIADDK administration has responded, in an outstanding and exemplary manner to the many complex demands placed upon it by the DD Program...a program which must keep pace with scientific progress concerning over 50 acute and chronic diseases ranging from appendicitis to liver disease and colon cancer. As a result, significant advances have been made in our understanding of digestive diseases such as inflammatory bowel disease.

Under the extraordinary, innovative and talented stewardship of Vay Liang W. Go., MD, we can with certainty predict that the DD Program, if permitted the strong focus it now has, will become ever more responsive to the needs of this complex and comprehensive range of basic and clinical research investigations.

We strongly commend all of Dr. Go's recent efforts to keep current with research progress by realigning the administration of the DD Divsion. We applaud as well the efforts of Mr. Earl Laurence who serves with intelligence and fairness in an environment requiring "Solomon-like" ability to keep the many important programs at the NIDDK on an equitable and productive basis.

It is only because of the DD Sub-Council of the NIADDK, the DD Advisory Board, the Clearinghouse and the well directed NIH Research Program that we have achieved as much as we have these last 10 years.

(over)

It is only with a strong and visible focus on the Digestive Diseases Program within the NIDDK that we can be assured of its continuing responsiveness and success. This focus must not be interrupted. It must not be diluted or integrated within any research program at the NIH if we are to stay on this commendable journey.

Sincerely,

Suzanne Rosenthal

Suzanne Rosenthal
National President

cc: Vay Liang W. Go, MD

SR:mf

Parent Council for Growth Normality
825 North Main Street
Opelousas, Louisiana 70570
a non-profit corporation

Summary of Testimony to the Committee for Administrative Review of Programs of the NIDDKD

by the
Parent Council for Growth Normality

I. Crisis in treatment with pituitary-derived human growth normone (hGH)
   A. Contamination of hGH by Creutzfeldt-Jakob disease (CJd)
   B. Relation to NIDDKD programs
      1. National Hormone and Pituitary Program (NHPP)
   C. Availability of information and support to effected families
   D. Effect of crisis on children and families

II. Response to hGH crisis by NIDDKD/NHPP
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III. Conclusions and recommendations
   A. Adequacy of response
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      3. Oversight structure
   C. Recommendations

Digestive
Disease
National
Coalition

(formerly Coalition of Digestive Disease Organizations)

1825 Eye Street, NW, Suite 400, Washington, DC 20006
(202) 429-2073

I am John Farrar, a physician and President of the Digestive Disease National Coalition. This Coalition, representing 20 professional and lay organizations, would like to express its complete accord with the administration of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

The Coalition feels that the NIDDK is an excellent locus for the scientific programs on digestive diseases for two reasons:

1. The scientific principles of metabolism, renal diseases, diabetes, hematology and digestive diseases share many similarities and, we are told, very healthy scientific cooperation exists between investigators in these disciplines.
2. Under the direction of Dr. Vay Liang Go, the Director of the Division of Digestive Diseases and Nutrition, the programs in digestive disease and nutrition have been reorganized and are functioning superbly.

It is clear to us that any further shifts of programs from this Institute would be divisive and would severely impair scientific productivity.

I should add that the DDNC earnestly hopes that the costs of setting up and administering the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) will not substantially deplete the resources of the NIDDK. Such a depletion would subvert the intent of Congress.

Thank you for allowing me the privilege of presenting the views of our organizations.

John T. Farrar

JOHN T. FARRAR, M.D.

THE ENDOCRINE SOCIETY

OFFICE OF THE EXECUTIVE DIRECTOR
9650 ROCKVILLE PIKE
BETHESDA, MARYLAND 20814
TELEPHONE (301) 530-9660

June 26, 1986

Dr. James B. Wyngaarden
Director, National Institutes of Health
Building 1
National Institutes of Health
Bethesda, MD 20892

Dear Dr. Wyngaarden:

In response to the invitation of the Committee for Administrative Review of the Program of the National Institute of Diabetes and Digestive and Kidney Disease, the President, Council, and Membership of The Endocrine Society wish to communicate their views concerning the appropriateness of the present structure of the NIDDK.

We believe strongly that the present array of programs and administrative structures of NIDDK should be preserved and strengthened, since the present framework already provides an effective, unified and highly successful synergistic basis for existing research efforts in hematology, diabetes, endocrinology, gastroenterology and nephrology, fields of study which are naturally interrelated through a common preoccupation with metabolism.

There is a natural affinity among the biological themes that underly and motivate current research programs within the existing Institute, for example, metabolic regulation and endocrine, paracrine and autocrine intercellular signalling in the physiology and pathophysiology of digestive, renal, hematopoeitic and endocrine organs. Administrative and program efficiency results from natural linkages among the four areas in which mutual interests are presently shared through such activities as workshops on methods and joint distribution of critical research materials.

To strengthen further the current organizational structure, we believe it is imperative that a Director of the Institute with established leadership qualities be rapidly chosen and confirmed, that adequate administrative staffing be established, and that future increases in fiscal appropriations to adequate levels be stoutly promoted. Removal of any existing scientific

ES/NIH Distr. 7/1/86 - ADPPE - DIK/NIH Sig. (due 7/15)
Info cys: Wyngaarden, Malone, Beaven, NIDDK

programs, we think, would more likely fragment and reduce - not improve - current scientific program effectiveness by disrupting the synergy now prevailing - a major source of institutional strength.

Sincerely yours,

Sidney H. Ingbar
President

Statement of Russell W. Chesney, M.D.
Professor and Vice Chair
University of California Davis

I appear before you today to represent investigators in pediatrics departments and to represent pediatric nephrologists whose efforts fall within the purview of the mission of the NIDDK. I currently serve as the President of the Society for Pediatric Research and as the President of the American Society of Pediatric Nephrology and have been asked by these societies to provide public testimony at this meeting.

Grants to pediatric investigators since the inception of this Institute under its many names have been substantial and have produced many advances in our knowledge of genetic disorders affecting the gastrointestinal tract and kidney, ~~of~~ in cystic fibrosis, in the area of diabetes, endocrinology and metabolic disease. Major breakthroughs have recently been made by members of the Society of Pediatric Research in understanding the molecular mechanism of a variety of conditions such as cystinosis, cystic fibrosis, hypophosphatemic rickets, urea cycle defects and phenylketonuria by grants from the NIDDK. Other grants support such projects as the pathogenesis and treatment of childhood renal osteodystrophy, the dietary needs for young children with chronic renal failure, the control of growth-promoting hormones in the young and the regulation of the synthesis of and action of growth promoting hormones such as the somatomedins. It is our hope that as the scope of the new NIDDK is reviewed as required by Public Law 99-158 that these and other programs will continue to have full and sufficient support of the Institute.

Members of the American Society of Pediatric Nephrology have also benefited from the programs of the NIDDK. We now have a clearer understanding

of fetal and neonatal physiology, of the nutrition requirements of the young child with uremia, the nature of diabetic nephropathy and the studies mentioned previously.

We perceive four areas that need emphasis as this review is taking place. First, the area of developmental renal physiology is of importance. A better understanding of developmental renal physiology will enhance the capacity of pediatricians to deal with problems that are found in the neonatal nursery, to better appreciate the problems encountered in the young child undergoing cardiac or other forms of surgery, to understand early factors in the development of hypertension and uremia in adulthood.

Second we see the need to emphasize congenital and genetic diseases of the kidney such as IgA-IgG nephropathy, diabetes, cystinosis, and reflux nephropathy as well as the various polycystic renal diseases that start during childhood.

Third, the requirements of the child undergoing a renal transplant need to be better understood. We need to understand the physiologic reasons that young kidneys may not be the best type of kidney to use and to develop methods to improve their function to determine whether early transplantation (at a young age) will improve the growth, mental development and rehabilitation of children with congenital renal conditions, whether protocols employing cyclosporin will produce better growth than those employing prednisone as an immunosuppressant agent and a better appreciation of the mechanism of donor-specific transfusions.

Testimony given at NIDDK, NIH

Dr. James Allen Olson
President, American Institute of Nutrition

1 July 1986

It is a pleasure for me to appear before this distinguished group in order to present some views about possible positive developments in the science of nutrition at the National Institutes of Health. Unfortunately, the splitting of NIADDK, about which I'm sure you have mixed feelings, has provided the context in which this opportunity has arisen. I am here, by the way, as the president of the American Institute of Nutrition, and I wish to introduce as well Dr. Richard Allison, Executive Officer of the Institute, whose office is just next door on the FASEB campus.

In my brief remarks, I wish to consider four points:

1) the nature of the scientific nutritional community in the U.S.,
2) the current state of nutrition at NIH, as viewed by an outside observer,
3) some hazards that imperil nutritional science, and finally,
4) some recommendations for your consideration.

Let's deal first with the nature of nutritional science. Nutrition is a very diffuse area, which is both its charm and, in a sense, its downfall. Within the United States the American Institute of Nutrition (AIN), and its sister society, the American Society for Clinical Nutrition (ASCN), are the primary scientific sector of a much vaster nutritional community. The research community in nutrition, both basic and clinical, is currently vigorous and fairly extensive, and I naturally hope that that situation will not only continue but also will improve. Within the United States, therefore, these two societies, AIN and ASCN, represent the largest part, although obviously not all, of the research community involved in aspects of nutrition which should be of particular interest to NIH.

Now I wish to give an outsider's view of the current state of nutrition at NIH, dealing separately with your intramural and extramural programs. Intramurally, few nutritional scientists work at NIH, and those that do tend to be oriented towards specific programs such as cancer, bone disease and child health. It is therefore, a very diffuse resident community. A few years ago a nutritional coordinating committee was established to serve as a focus for all such activities. Coordination across administrative lines is never easy, but at least nutrition received some prominence. Nonetheless, a major concern that we outsiders harbor is that nutrition lacks both a home and a powerful specific voice at NIH. Extramurally, we in the outside research community greatly appreciate the support that NIH has given over the years, both to basic and to clinical research, including the development of the clinical nutrition research units (CNRU's). When times were good, we had no cause for alarm. But budget cuts cause everyone to suffer, and unquestionably those

(NINDDK). Such a change will do much for the Institute and for NIH, and further and most importantly, it will give nutrition a home within this marvelous research institution.

Second, an Associate Director of Nutrition should be appointed within the Institute. Now I know that Dr. Go has taken on this task, and he is reputed to be a very fine administrator and scientist. But if one has too many different things to do, it is very difficult to handle all of them equally well. So the presence of a specific strong voice in nutrition itself at a high level within the Institute and within the NIH administration is really essential.

Third, the coordination and communication of nutritional activities across Institutes at NIH should continue. During this transitional phase, that activity might well be carefully reassessed and strengthened.

Fourth, support for the important place of nutrition in health and disease should be tangibly expressed. But I should also sound a note of caution. With the current high interest in nutrition, many "instant" nutritionists, i.e. individuals with no credentials in nutritional science but who claim great expertise and hold lofty, often self-aggrandizing views, have suddenly appeared. NIH should painstakingly separate the chaff from the grain.

Finally, in the splitting of NIADDK, NIH should be careful that key nutritional areas, such as those of calcium and vitamin D, don't fall between the cracks.

JAO/jnw

SUMMARY OF COMMENTS BEFORE A COMMITTEE CONDUCTING AN ADMINISTRATIVE REVIEW OF THE DISEASE RESEARCH PROGRAMS OF THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES. July 1, 1986.

COMMENTS BY: James A. Olson, Ph.D.
President, American Institute of Nutrition

Richard G. Allison, Ph.D.
Science Officer, American Institute of Nutrition and
The American Society for Clinical Nutrition

The American Institute of Nutrition (AIN) and The American Society for Clinical Nutrition (ASCN) are the primary organizations of nutrition research scientists in the United States. The American Society for Clinical Nutrition (ASCN) is the clinical division of the AIN. A majority of the membership is university-based, involved in basic research. Members are nominated and elected by their fellow scientists on the basis of demonstrated research competence and productivity in the fields of experimental and clinical nutrition. The purposes of the Institute are to develop and extend knowledge of nutrition, to facilitate personal contact between investigators in nutrition and related fields of interest, and to recognize, through its awards, excellence in nutrition research and related accomplishments. Close organizational and working relationships are maintained with several other scientific societies for the purpose of jointly sponsored scientific meetings and information exchange. AIN is a member of the Federation of American Societies for Experimental Biology (FASEB), and its purposes are consisitent with those of the other five societies that make up the Federation, namely, the American Physiological Society, the American Society of Biological Chemists, the American Society for Pharmacology and Experimental Therapeutics, the American Association of Pathologists and the American Association of Immunologists.

The interests and concerns of the professional nutritionists whom our societies represent transcend the institutional structure of the NIH and that of other federal agencies and private institutions engaged in the support of biomedical research. We recognize the difficulty of the task being undertaken by your comittee and wish to support you in your efforts which should result in fostering creative scientific research most efficiently within an evolving administrative structure. Our societies have watched with great interest changes in both the apparent direction of nutrition programs and the institutional setting of these efforts within NIH.

The professional nutrition research community would welcome tangible evidence of a continuing administrative committment to the importance of nutrition at the highest level possible within NIH. The fate of nutrition within basic and clinical research programs should not be dependent on the personal initiatives of individual employees in the absence of an appropriate administrative structural mandate. Supportive evidence might include identification of nutrition within the name of this Institute, a reexamination of recommendations for an Associate Director for Nutrition, and implementation of strengthened and innovative programs such as the clinical Nutrition Research Centers and the Clinical Nutrition Scientist Program.

Four, we see the need to support studies that examine diseases or disease processes that develop during childhood, but which become apparent in adult life. Among these are hypertension, polycystic renal disease, ~~osteoporosis~~ renal stone disease, many glomerulonephropathies, diabetes mellitus and reflux nephropathy. Our knowledge concerning the etiology and ultimate pathogenesis of these conditions can only come from studies aimed at an appreciation of the beginning of these disorders.

As a final word, pediatric investigators have flourished in this country due to their efforts and the support of the NIDDK. Our numbers are small and our representation on study sections is limited. However, our productivity has been great, our scientific insights meaningful and our goals worthy of support. We hope that this review of the NIDDK will understand our needs and goals and will continue to support our efforts.

COOLEY'S ANEMIA FOUNDATION, INC.
SUITE 911 • 105 EAST 22nd STREET, NEW YORK, NEW YORK 10010 • (212) 598-0911

June 9, 1986

Thomas E. Malone, Ph.D.
Chairman
Committee for Administrative Review
of the Programs of NIDDK
132 Building 1
Bethesda, MD 20892

Dear Dr. Malone,

Subject: ATTACHED LETTER TO DR. WYNGAARDEN REGARDING CONTINUATION OF HEMATOLOGY PROGRAM IN NIDDK

It is our understanding that you are Chairman of the Committee for the Administrative Review of the Programs of the NIDDK.

We would like to go on record most strongly as supporting the continuation of the hematology program in the NIDDK, because of its massive benefits for the Cooley's Anemia patient population.

Please find attached a copy of a letter that was sent to Dr. Wyngaarden on April 15, 1986 in that regard.

I am taking the liberty of sending a copy of this along to Mr. Edward Lynch of the NIH.

Thank you for your consideration.

Sincerely yours,

Mike DiFilippo

Michael DiFilippo
Executive Director

COOLEY'S ANEMIA FOUNDATION, INC.
SUITE 911 • 105 EAST 22nd STREET, NEW YORK, NEW YORK 10010 • (212) 598-0911

April 15, 1986

James Wyngaarden, M.D.
Director
National Institutes of Health
124 Building 1
Bethesda, MD 20892

Dear Dr. Wyngaarden,

Subject: HEMATOLOGY PROGRAM IN THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

It is our understanding that as a result of the NIH biomedical research authorization legislation passed by the Congress last year, you were requested by the Congress to study the structure of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to see whether any programs currently in that Institute would be more efficient if transferred to other institutes.

We would like you to know that the Cooley's Anemia Foundation Board of Directors solidly supports, in the strongest possible way, the continuation of the hematology program in the NIDDK.

We also want you to know that the leadership of that Institute has always been very supportive of the Cooley's Anemia Foundation, and at times have met with our organization at our national meetings in New York, which are always held on Saturday morning. They have been extraordinarily helpful in helping our medical research personnel to understand on-going research that is being undertaken through that Institute's funding. We have the highest praise for the work of Dr. Gary Striker, who heads the Kidney, Urology, Hematology cluster of programs, and also especially Dr. David Badman, who has consistently worked with us in establishing information programs so that all of our volunteers are made aware of the progress being made.

Therefore, Dr. Wyngaarden, we stand 100% behind the continuation of the hematology program in that Institute.

We are taking the liberty of sending a copy of this letter along to Dr. David Nathan, President of the American Society of Hematology, and a very compassionate and hard-working physician, who has been very helpful to Cooley's Anemia patients, to let him know that we support the position of the Society in regard to support for the hematology program.

If you have any questions on this matter, please call or write me at the address and phone number on this letterhead.

Thank you very much.

Sincerely yours,

Mike DiFilippo

Michael DiFilippo
Executive Director

Cystic Fibrosis Foundation
National Office
6000 Executive Boulevard • Rockville, Maryland 20852
(301) 881-9130

June 24, 1986

Thomas E. Malone, Ph.D.
Deputy Director of the NIH
Building 1, Room 132
Bethesda, Maryland 20892

Dear Dr. Malone:

Thank you for your recent letter offering the Cystic Fibrosis Foundation the opportunity to participate in the administrative review of the organizational structure of the newly reorganized National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK).

The Cystic Fibrosis Foundation has enjoyed a long lasting affiliation with both the intramural and extramural programs of the NIDDK. In cooperation with the National Heart, Lung, and Blood Institute (NHLBI), the NIDDK sponsored the congressionally mandated study in the late 1970s, which called for the creation of the research environments that are making the major contributions to the understanding of this disease today.

Since the report was submitted to the Congress, the Foundation has continued to be appreciative of the efforts of the NIDDK and the NHLBI as well as those of the other institutes involved in CF research, including the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of General Medical Sciences (NIGMS). The cooperation and communication among these institutes have been reflected in the co-sponsorship of a number of conferences and projects over the past several years.

We will continue to look forward to working with these institutes in the future. Since the CF program of the NIDDK has been administered through the Division of Diabetes, Endocrinology and Metabolic Diseases, we cannot identify any adverse factors that will result from the restructuring of the institute.

We appreciate the NIH's continued interest in the activities of the Foundation.

Sincerely,

Robert K. Dresing
President and C.E.O.

Rainbow Babies &
Childrens Hospital
University Hospitals of Cleveland
2074 Abington Road
Cleveland, Ohio 44106
216-844-1000

Rainbow Babies and Childrens Hospital

Pulmonary Disease Center
216-844-3267

Infant APNEA/SIDS Center
216-844-1301

Asthma Center
216-844-8777

July 1, 1986

Dr. Jay Moskowitz
Associate Director for Program
Planning and Evaluation
Office of the Director
National Institutes of Health
Building 1, Room 137
Bethesda, Maryland 20892

Dear Dr. Moskowitz:

I have been asked by Dr. Nancy Lamontagne, the program administrator for our Core Center Grant in Cystic Fibrosis, to write to you and tell you how the Cystic Fibrosis Core Center at Case Western Reserve University has worked under the aegis of the NIDDK. This particular grant mechanism suits our center well. The Center Grant itself funds five administrative and scientific cores which promote cost saving, resource sharing and communication among our investigators. These cores support efforts of RO1 grants (from the NIDDKD, NHLBI, NIAID, NIGMS) which total over $2 million (direct costs). In addition, the Core Center supports pilot and feasibility studies, and we have local start-up funds for pilot studies as well. This structure has resulted in an extremely productive and active center with both mature and developing projects.

The flexibility of the Core Center mechanism and its enlightened administration by the NIDDK have been especially important in the last year, in which I took over as Center Director and made major changes in the structure of the Center to improve productivity and streamline the cores. The NIDDK administrators were extremely helpful in recognizing the unique strengths of our program and assisting me in rearranging the budgets and the structure to capitalize on them. Since the reorganization took place six months ago, core utilization has been excellent and productivity has increased. I have received excellent cooperation and assistance from the NIDDK staff and look forward to continued cordial relations with them.

I hope this information is helpful to you in assessing the success of the CF program in the NIDDK.

Sincerely,

Pamela B. Davis, M.D., Ph.D.
Chief, Pediatric Pulmonary Division

PBD/kt

NATIONAL DIGESTIVE DISEASES ADVISORY BOARD

1801 Rockville Pike
Suite 500
Rockville, Maryland 20852

Telephone
301-496-6045

June 30, 1986

Thomas E. Malone, Ph.D.
Chairman
Committee for the Administrative
Review of the Programs for NIDDK
National Institutes of Health
Shannon Building, Room 132
Bethesda, Maryland 20892

Dear Dr. Malone:

I am Dr. Donald E. Wilson, Professor and Chairman of the Department of Medicine, State University of New York Health Science Center at Brooklyn. I am writing to you as Chairman of the National Digestive Diseases Advisory Board with respect to the administrative review of the programs of NIDDK, public hearings to occur on July 1, 1986. While the Board does not feel that it is necessary for me to testify in person at the hearings, we do wish to provide you with our input.

At this point in time there does not appear to be any advantage to further restructuring of NIDDK. The Board firmly supports maintaining the present administrative structure of NIDDK and would argue against any further separation of individual components. We are quite concerned, however, that the establishment of the new NIAMS has not been accompanied by appropriate administrative support. Since the staff of the former NIADDK has been required to provide simultaneous support to both NIDDK and the new NIAMS, the NIDDK is now seriously compromised with respect to its ability to effectively and appropriately administer the scientific programs under it purview. During the congressional hearings incidental to the establishment of NIAMS, it was well documented that additional administrative resources and personnel would be needed to operate the new Institute. There was a consensus that $3.5 million and 36 new positions were needed for this purpose. These resources have not been provided. It will be impossible to operate the two Institutes solely by a reallocation of existing personnel since the size of the administrative staff of the former NIADDK was already significantly smaller than that of almost every other NIH Institute in relationship to the size of their respective programs.

The NDDAB firmly believes that it is essential that increased administrative resources be provided to both NIDDK and NIAMS in order to prevent a serious

compromise of our research efforts. Certainly the establishment of additional separate administrative units should not be considered until such time as appropriate support is available for existing units.

On behalf of the NDDAB, I appreciate the opportunity to write to you and the committee and appreciate your consideration of our views.

Sincerely,

Donald E. Wilson, M.D.

Ed. Lynch

American Diabetes Association., Inc.

National Service Center 1660 Duke Street Alexandria, Virginia 22314 (703) 549-1500 Telex: 901132

May 30, 1986

Thomas E. Malone, Ph.D.
National Institutes of Health
NIDDK
Shannon Building, Room 132
Bethesda, MD 20892

Dear Dr. Malone,

The American Diabetes Association appreciates the opportunity to respond to your letter requesting our views on the administrative effectiveness of the NIDDK.

We believe that the current administrative structure of the NIDDK is extremely well-managed and organized. Having worked closely for many years with most of the administrative officers of the NIDDK, particularly those in the Division of Diabetes, Endocrinology and Metabolic Disease, we are very impressed with their efficiency and effectiveness. We do not feel that there is any more appropriate or able component of the NIH that would better administer any of the programs of the NIDDK.

In fact, we believe that the administrative functions of the NIDDK are conducted far more effectively than one would expect, given the very limited number of staff in the Institute. The Division of Diabetes, Endocrinology and Metabolic Disease, for example, has too few staff for the size and number of programs it manages and we strongly recommend that consideration be given to increasing their staff size.

We recognize that federal budget cutbacks have significantly hurt the administrative functions of the entire NIH. With the recent realignment of the NIDDK, we trust that the administrative support for the Institute will not be penalized out of proportion to the programs lost. Moreover, we hope that the Division of Diabetes, Endocrinology and Metabolic Disease, which will now comprise more than 50% of the Institute's budget, has administrative resources commensurate with their size.

We also wish to inform you that Dr. Richard Kahn, from our National Service Center staff, will be attending the July 1st meeting as an observer.

Thank you for considering our comments.

Sincerely,

Harold Rifkin

Harold Rifkin, M.D.
President

HR/fg